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(54) Title: TRP8, TRP9 AND TRP10, NOVEL MARKERS FOR CANCER

(57) Abstract: The present invention relates to gene expression in normal cells and cells of malignant tumors and particularly to novel markers associated with cancer, Trp8, Trp9 and Trp10, and the genes encoding Trp8, Trp9 and Trp10. Also provided are vectors, host cells, antibodies, and recombinant methods for producing these human proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating a tumor.

Trp8, Trp9 and Trp10, novel markers for cancer

FIELD OF THE INVENTION

The present invention relates to gene expression in normal cells and cells of malignant tumors and particularly to novel markers associated with cancer, Trp8, Trp9 and Trp10, and the genes encoding Trp8, Trp9 and Trp10

BACKROUND OF THE TECHNOLOGY

Prostate cancer is one of the most common diseases of older men world wide. Diagnosis and monitoring of prostate cancer is difficult because of the heterogeneity of the disease. For diagnosis different grades of malignancy can be distinguished according to the Gleason-Score Diagnosis. For this diagnosis a prostate tissue sample is taken from the patient by biopsy and the morphology of the tissue is investigated. However, this approach only yields subjective results depending on the experience of the pathologist. For confirmation of these results and for obtaining an early diagnosis an additional diagnostic method can be applied which is based on the detection of a prostate specific antigen (PSA). PSA is assayed in serum samples, blood samples etc. using an anti-PSA-antibody. However, since in principle PSA is also expressed in normal prostate tissue there is a requirement for the definition of a threshold value (about 4 ng/ml PSA) in order to be able to distinguish between normal and malign prostate tissue. Unfortunately, this diagnostic method is quite insensitive and often yields false-positive results. Moreover, by using this diagnostic method any conclusions as regards the grade of malignancy, the progression of the tumor and its potential for metastasizing cannot be drawn. Thus, the use of molecular markers would be helpful to distinguish benign from malign tissue and for grading and staging prostate carcinoma, particularly for patients with metastasizing prostate cancer having a very bad prognosis.

The above discussed limitations and failings of the prior art to provide meaningful specific markers which correlate with the presence of prostate tumors, in particular metastasizing tumors, has created a need for markers which can be used diagnostically, prognostically and therapeutically over the course of this disease. The present invention fulfils such a need by the provision of Tpr8, Trp9 and Trp10 and the genes encoding Trp8, Trp9 and Trp10: The genes encoding Trp8 and Trp10 are expressed in prostate carcinoma and prostatic metastasis, but

not in normal prostate, benign hyperplasia (BHP) and intraepithelial prostatic neoplasia (PIN). Furthermore, expression of Trp10 transcripts is detectable in carcinoma but not in healthy tissue of the lung, the prostate, the placenta and in melanoma.

SUMMARY OF THE INVENTION

The present invention is based on the isolation of genes encoding novel markers associated with a cancer, Trp8, Trp9 and Trp10. The new calcium channel proteins Trp8, Trp9 and Trp10 are members of the trp (transient receptor potential) - family, isolated from human placenta (Trp8a and Trp8b) and humane prostate (Trp9, Trp10a and Trp10b). Trp proteins belong to a steadily growing family of Ca²⁺ selective and non selective ion channels. In the recent years seven Trp proteins (trp1 - trp7) have been identified and suggested to be involved in cation entry, receptor operated calcium entry and pheromone sensory signaling. Structurally related to the trp proteins are the vanilloid receptor (VR1) and the vanilloid like receptor (VRL-1) both involved in nociception triggered by heat. Furthermore, two calcium permeable channels were identified in rat small intestine (CaT1) and rabbit kidney (ECaC). These distantly related channels are suggested to be involved in the uptake of calcium ions from the lumen of the small intestine (CaT1) or in the reuptake of calcium ions in the distal tubule of the kidney (ECaC). Common features or the Trp and related channels are a proposed structure comprising six transmembrane domains including several conserved amino acid motifs. In the present invention the cloning and expression of a CaT1 like calcium channel (Trp8) from human placenta as well as Trp9 and Trp10 (two variants, Trp10a and Trp10b) is described. Two polymorphic variants of the Trp8 cDNA were isolated from placenta (Trp8a and Trp8b). Transient expression of the Trp8b cDNA in HEK (human embryonic kidney) cells results in cytosolic calcium overload implicating that the Trp8 channel is constitutive open in the expression system. Trp8 induces highly calcium selective inward currents in HEK cells. The C-terminus of the Trp8 protein binds calmodulin in a calcium dependent manner. The Trp9 channel is expressed in trophoblasts and syncytiotrophoblasts of placenta and in pancreatic acinar cells. Furthermore, the Trp8 channel is expressed in prostatic carcinoma and prostatic metastases, but not in normal tissue of the prostate. No expression of Trp8 transcripts is detectable in benign prostatic hyperplasia (BPH) or prostatic intraepithelial neoplasia (PIN). Therefore, the Trp8 channel is exclusively expressed in malign prostatic tissues and serves as molecular marker for prostate cancer. From the experimental results it is also apparent that the

modulation of Trp8 and/or Trp10, e.g. the inhibition of expression or activity, is of therapeutic interest, e.g. for the prevention of tumor progression.

The present invention, thus, provides a Trp8, Trp9 and Trp10 protein, respectively, as well as nucleic acid molecule encoding the protein and, moreover, an antisense RNA, a ribozyme and an inhibitor, which allow to inhibit the expression or the activity of Trp8, Trp9 and/or Trp10.

In one embodiment, the present invention provides a diagnostic method for detecting a prostate cancer or endometrial cancer (cancer of the uterus) associated with Trp8 or Trp10 in a tissue of a subject, comprising contacting a sample containing Trp8 and/or Trp10 encoding mRNA with a reagent which detects Trp8 and/or Trp10 or the corresponding mRNA.

In a further embodiment, the present invention provides a diagnostic method for detecting a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense transcripts or Trp10a and/or Trp10b related antisense transcripts.

In another embodiment, the present invention provides a method of treating a prostate tumor, carcinoma of the lung, carcinoma of the placenta (chorion carcinoma) or melanoma associated with Trp8 and/or Trp10, comprising administering to a subject with such an disorder a therapeutically effect amount of a reagent which modulates, e.g. inhibits, expression of Trp8 and/or Trp10 or the activity of the protein, e.g. the above described compounds.

Finally, the present invention provides a method of gene therapy comprising introducing into cells of a subject an expression vector comprising a nucleotide sequence encoding the above mentioned antisense RNA or ribozyme, in operable linkage with a promoter.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: A, phylogenetic relationship of trp and related proteins. B, hydropathy plot of the Trp8 protein sequence according to Kyte and Doolittle. C, alignment of Trp8a/b to the epithelial calcium channels ECaC (from rabbit) and Vr1 (from rat). Putative transmembrane domains are underlined.

Figure 2: A, polymorphism of the Trp8 gene. The polymorphic variants Trp8a and Trp8b differ in five base pairs resulting in three amino acid exchanges in the derived protein sequences. Specific primers were derived from the Trp8 gene as indicated by arrows. B, the Trp8a and Trp8b genes are distinguishable by a single restriction site. Genomic fragments of the Trp8 gene can be amplified using specific primers (shown in A). The genomic fragment of the Trp8b gene contains an additional site of the restriction enzyme BSP1286I (B). C, the Trp8 gene is located on chromosome 7. D, genotyping of eleven human subjects. A 458 bp genomic fragment of the Trp8 gene was amplified using specific primers (shown in A) and restricted with BSP1286I. The resulting fragments were analyzed by PAGE electrophoresis.

Figure 3: The Trp8b protein is a calcium selective ion channel. A, representative trace of a pdiTrp8b transfected HEK 293 cell. Trp8b mediated currents are activated by voltage ramps (-100 mV - +100 mV) of 100 msec at -40 mV or +70 mV holding potential. 1, Trp8b currents in the presence at 2mm $[Ca^{2+}]_0$; 2, effect of solution switch alone 3, switch to nominal zero calcium solution. B, Trp8b currents in the presence of zero divalent cations. C, current voltage relationship of the currents shown in A. Inset, leak subtracted current. D, current voltage relationship of the current shown in B. E, statistics of representative experiments. Black: Trp8 transfected cells, gray: control cells. Columns from left to right: Trp8 currents at - 40 mV (n=12) and +70 mV holding potential (n=12). Trp8 currents in standard bath solution including 120 mM NMDG without sodium (n = 7) and with nominal zero calcium ions (n = 8) or in the presence of 1mM EGTA with zero divalent cations (n = 6). F, representative changes in $[Ca^{2+}]_0$ in Trp8b transfected HEK cells (gray) and controls (black) in the presence or absence of 1mM $[Ca^{2+}]_0$. Inset, relative increase of cytosolic calcium concentration of Trp8b transfected HEK cells, before and after readdition of 1 mM $[Ca^{2+}]_0$ in comparison to control cells.

Figure 4: The C-terminal region of the Trp8 protein binds calmodulin. A, N- and C-terminal fragments of the Trp8 protein used for calmodulin binding studies. B, the Trp8 protein and a truncated Trp8 protein which was in vitro translated after MunI cut of the cDNA, which lacks the C-terminal 32 amino acid residues, were in vitro translated in the presence of ³⁵S-methionine and incubated with calmodulin coupled agarose beads in the presence of 1 mM Ca²⁺ or 2 mM EGTA. C, calmodulin binding to N- and C-terminal fragments of the Trp8protein in the presence of Ca²⁺ (1 mM) or EGTA (2 mM)

Figure 5: Expression pattern of the Trp8 cDNA. A, Northern blots (left panels, Clontech, Palo Alto) were hybridized using a 348 bp NcoI/BamHT fragment of the Trp9 cDNA. The probe hybridizes to mRNA species isolated from the commercial blot, but not to mRNA species isolated from benign prostate hyperplasia (right panel, mRNA isolated from 20 human subjects with benign prostate hyperplasia). B,C, in situ hybridization with biotinylated Trp8 specific oligonucleotides on slides of human tissues. Left column antisense probes, right column sense probes. D, antinsense probes.

Figure 6: Differential expression of Trp8 cDNA in human prostate. A-F, in situ hybridization with prostatic tissues. A, normal prostate, B, primary carcinoma, C, benign hyperplasia, D, rezidive carcinoma, E, prostatic intraepithelial neoplasia, F, lymphnode metastasis of the prostata.

Figure 7: Trp8a cDNA sequence and derived amino acid sequence

Figure 8: A, Trp8b cDNA sequence and derived amino acid sequence

B, cDNA sequence of splice variant 1 (12B1)

C, cDNA sequence of splice variant 2 (17-3)

D, cDNA sequence of splice variant 3 (23A3)

E, cDNA sequence of splice variant 4 (23C3)

Figure 9: A, Trp9 cDNA sequence and derived amino acid sequence B, cDNA sequence of splice variant 15 and derived amino acid sequence.

Figure 10: A, cDNA sequence of Trp10a and derived amino acid sequence, B, cDNA fragment of Trp10a and derived amino acid sequence.

Figure 11: cDNA sequence of Trp10b and derived amino acid sequence.

Figure 12: Expression of Trp8 mRNA in human endometrial cancer or cancer of the uterus. A - D, in situ hybridization with slides of endometrial cancer hybridized with Trp8 antisense (left column) or sense probes as controls (right column). E - F, Trp8 antisense probes hybridized to slides of normal endometrium. It can be clearly seen no hybridization occurs with normal endometrial tissue.

Figure 13: Expression of human Trp9 and Trp10 genes

Northern blots were hybridized using Trp9 (upper panel) or Trp10 (lower panel) specific probes. Expression of the Trp9 cDNA is detectable in many tissues including human prostate and colon as well as in benign prostatic hyperplasia. Expression of Trp10 cDNA is detectable in human prostate of a commercial northern blot (Clontech, right side). This Northern blot contains prostatic tissue collected from 15 human subjects in the range of 14 - 60 years of age. No expression of Trp10 cDNA was detectable in benign prostatic hyperplasia (left side).

Figure 14: Expression of Trp10 transcripts and Trp10-antisense transcripts in human prostate cancer and metastasis of a melanoma. In situ hybridizations of slides hybridized with Trp10-antisense (A-E, K-N) and Trp10 related sense probes (F-J, P-R). It can clearly be seen that both probes detect the same cancer cells indicating that these cancer cells express Trp10 transcripts as well as Trp10-antisense transcripts. S, no Trp10 expression is detectable in benign hyperplasia of the prostate (BPH). O and T, show expression of Trp10 transcripts (O) and Trp10-antisense transcripts (T) in a metastasis of a melanoma in human lung. Melanoma cancer cells express both Trp10 transcripts and Trp10-antisense transcripts.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b or a protein exhibiting biological properties of Trp8a, Trp8b, Trp9, Trp10a or Trp10b and being selected from the group consisting of

- (a) a nucleic acid molecule encoding a protein that comprises the amino acid sequence depicted in Figure 7, 8A, 9,10 or 11;
- (b) a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A, 9,10, or 11;
- (c) a nucleic acid molecule included in DSMZ Deposit no. DSM 13579 (deposit date: 28 June 2000), DSM 13580 (deposit date: 28 June 2000), DSM 13584 (deposit date: 5 July 2000), DSM 13581 (deposit date: 28 June 2000) or DSM(deposit date:....);
- (d) a nucleic acid molecule with hybridizes to a nucleic acid molecule specified in (a) to (c)

(e) a nucleic acid molecule the nucleic acid sequence of which deviates from the nucleic sequences specified in (a) to (d) due to the degeneration of the genetic code; and

(f) a nucleic acid molecule, which represents a fragment, derivative or allelic variation of a nucleic acid sequence specified in (a) to (e).

As used herein, a protein exhibiting biological properties of Trp8a, Trp8b, Trp9,Trp10a or Trp10b is understood to be a protein having at least one of the activities as illustrated in the Examples, below.

As used herein, the term "isolated nucleic acid molecule, includes nucleic acid molecules substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with which it is naturally associated.

In a first embodiment, the invention provides an isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b comprising the amino acid sequence depicted in Figure 7, 8A, 9,10 or 11. The present invention also provides a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A, 9,10 or 11.

The present invention provides not only the generated nucleotide sequence identified in Figure 7, 8A, 9,10 or 11, respectively and the predicted translated amino acid sequence, respectively, but also plasmid DNA containing a Trp8a cDNA deposited with the DSMZ, under DSM 13579, a Trp8b cDNA deposited with the DSMZ, under DSM 13580, a Trp9 cDNA deposited with the DSMZ, under DSM 13581, and a Trp10b cDNA deposited with the DSMZ, under DSM...., respectively. The nucleotide sequence of each deposited Trp-clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by each deposited clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited Trp-encoding DNA, collecting the protein, and determining its sequence.

The nucleic acid molecules of the invention can be both DNA and RNA molecules. Suitable DNA molecules are, for example, genomic or cDNA molecules. It is understood that all

nucleic acid molecules encoding all or a portion of Trp8a, Trp8b, Trp9,Trp10a or Trp10b are also included, as long as they encode a polypeptide with biological activity. The nucleic acid molecules of the invention an be isolated from natural sources or can be synthesized according to know methods.

The present invention also provides nucleic acid molecules which hybridize to the above nucleic acid molecules. As used herein, the term "hybridize,, has the meaning of hybridization under conventional hybridization conditions, preferably under stringent conditions as described, for example, in Sambrook et al., Molecular Cloning, A Laboratory Manual 2nd edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. Also contemplated are nucleic acid molecules that hybridize to the Trp nucleic acid molecules at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency), salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°Cin a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 9.2M NaH₂PO₄; 0.02M EDTA, pH7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA, following by washes at 50°C with 1 X SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC). Variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Nucleic acid molecules that hybridize to the molecules of the invention can be isolated, e.g., from genomic or cDNA libraries that were produced from human cell lines or tissues. In order to identify and isolate such nucleic acid molecules the molecules of the invention or parts of these molecules or the reverse complements of these molecules can be used, for example by means of hybridization according to conventional methods (see, e.g., Sambrook et al., supra). As a hybridization probe nucleic acid molecules can be used, for example, that have exactly or basically the nucleotide sequence depicted in Figure 7, 8A, 9,10 or 11, respectively, or parts of these sequences. The fragments used as hybridization probe can be synthetic

fragments that were produced by means of conventional synthetic methods and the sequence of which basically corresponds to the sequence of a nucleic acid molecule of the invention.

The nucleic acid molecules of the present invention also include molecules with sequences that are degenerate as a result of the genetic code.

In a further embodiment, the present invention provides nucleic acid molecules which comprise fragments, derivatives and allelic variants of the nucleic acid molecules described above encoding a protein of the invention. "Fragments,, are understood to be parts of the nucleic acid molecules that are long enough to encode one of the described proteins. These fragments comprise nucleic acid molecules specifically hybridizing to transcripts of the nucleic acid molecules of the invention. These nucleic acid molecules can be used, for example, as probes or primers in the diagnostic assay and/or kit described below and, preferably, are oligonucleotides having a length of at least 10, in particular of at least 15 and particularly preferred of at least 50 nucleotides. The nucleic acid molecules and oligonucleotides of the invention can also be used, for example, as primers for a PCR reaction. Examples of particular useful probes (primers) are shown in Tables 1 and 2.

Table 1

Trp8 probes used for in situ hybridization:

Probes (antisense)

- 1.) 5' TCCGCTGCCGGTTGAGATCTTGCC 3'
- 2.) 5' CTTGCTCCATAGGCAGAGAATTAG 3'
- 3.) 5' ATCCTCAGAGCCCCGGGTGTGGAA3'

Controls (sense)

- 1.) 5' GGCAAGATCTCAACCGGCAGCGGA 3'
- 2.) 5' CTAATTCTCTGCCTATGGAGCAAG 3'
- 3.) 5' TTCCACACCCGGGGCTCTGAGGAT 3'

Tabelle 2

Trp10 probes used for the in situ hybridizations shown in Figure 14:

Probes (antisense)

1.) 5' GCTTCCACCCCAAGCTTCACAGGAATAGA 3' (Figure 14 A, 14B)

2.) 5' GGCGATGAAATGCTGGTCTGTGGC 3' (Figure 14C, 14D, 14N, 14S, 14O)

3.) 5' ATCTTCCAGTTCTTGGTGTCTCGG 3' (Figure 14E, 14K)

4.) 5' GCTGCAGTACTCCTGCACCAGGAA 3' (Figure 14L, 14M)

Probes (sense)

1.) 5' TCTATTCCTGTGAAGCTTGGGGTGGAAGC 3' (Figure 14F, 14G)

2.) 5' GCCACAGACCAGCATTTCATCGCC 3' (Figure 14H, 14I, 14T)

3.) 5' CCGAGACACCAAGAACTGGAAGAT 3' (Figure 14J, 14P)

4.) 5' TTCCTGGTGCAGGAGTACTGCAGC 3' (Figure 14Q, 14R)

The term "derivative, in this context means that the sequences of these molecules differ from the sequences of the nucleic acid molecules described above at one or several positions but have a high level of homology to these sequences. Homology hereby means a sequence identity of at least 40%, in particular an identity of at least 60%, preferably of more than 80% and particularly preferred of more than 90%. These proteins encoded by the nucleic acid molecules have a sequence identity to the amino acid sequence depicted in Figure 7, 8A, 9, 10 and 11, respectively, of at least 80%, preferably of 85% and particularly preferred of more than 90%, 97% and 99%. The deviations to the above-described nucleic acid molecules may have been produced by deletion, substitution, insertion or recombination. The definition of the derivatives also includes splice variants, e.g. the splice variants shown in Figures 8B to 8E and 9B.

The nucleic acid molecules that are homologous to the above-described molecules and that represent derivatives of these molecules usually are variations of these molecules that represent modifications having the same biological function. They can be naturally occurring variations, for example sequences from other organisms, or mutations that can either occur naturally or that have been introduced by specific mutagenesis. Furthermore the variations can be synthetically produced sequences. The allelic variants can be either naturally occurring variants or synthetically produced variants or variants produced by recombinant DNA processes.

Generally, by means of conventional molecular biological processes it is possible (see, e.g., Sambrook et al., supra) to introduce different mutations into the nucleic acid molecules of the invention. As a result Trp proteins or Trp related proteins with possibly modified biological properties are synthesized. One possibility is the production of deletion mutants in which nucleic acid molecules are produced by continuous deletions from the 5'- or 3'-terminal of the coding DNA sequence and that lead to the synthesis of proteins that are shortened accordingly. Another possibility is the introduction of single-point mutation at positions where a modification of the amino aid sequence influences, e.g., the ion channel properties or the regulations of the trp-ion channel. By this method muteins can be produced, for example, that possess a modified ion conducting pore, a modified K_m-value or that are no longer subject to the regulation mechanisms that normally exist in the cell, e.g. with regard to allosteric regulation or covalent modification. Such muteins might also be valuable as therapeutically useful antagonists of Trp8a, Trp8b, Trp9,Trp10a or Trp10b, respectively.

For the manipulation in prokaryotic cells by means of genetic engineering the nucleic acid molecules of the invention or parts of these molecules can be introduced into plasmids allowing a mutagenesis or a modification of a sequence by recombination of DNA sequences. By means of conventional methods (cf. Sambrook et al., supra) bases can be exchanged and natural or synthetic sequences can be added. In order to link the DNA fragments with each other adapters or linkers can be added to the fragments. Furthermore, manipulations can be performed that provide suitable cleavage sites or that remove superfluous DNA or cleavage sites. If insertions, deletions or substitutions are possible, in vitro mutagenesis, primer repair, restriction or ligation can be performed. As analysis method usually sequence analysis, restriction analysis and other biochemical or molecular biological methods are used.

The proteins encoded by the various variants of the nucleic acid molecules of the invention show certain common characteristics, such as ion channel activity, molecular weight, immunological reactivity or conformation or physical properties like the electrophoretical mobility, chromatographic behavior, sedimentation coefficients, solubility, spectroscopic properties, stability; pH optimum, temperature optimum.

The invention furthermore relates to vectors containing the nucleic acid molecules of the invention. Preferably, they are plasmids, cosmids, viruses, bacteriophages and other vectors

usually used in the field of genetic engineering. Vectors suitable for use in the present invention include, but are not limited to the T7-based expression vector for expression in mammalian cells and baculovirus-derived vectors for expression in insect cells. Preferably, the nucleic acid molecule of the invention is operatively linked to the regulatory elements in the recombinant vector of the invention that guarantee the transcription and synthesis of an RNA in prokryotic and/or eukaryotic cells that can be translated. The nucleotide sequence to be transcribed can be operably linked to a promoter like a T7, metallothionein I or polyhedrin promoter.

In a further embodiment, the present invention relates to recombinant host cells transiently or stable containing the nucleic acid molecules or vectors or the invention. A host cell is understood to be an organism that is capable to take up *in vitro* recombinant DNA and, if the case may be, to synthesize the proteins encoded by the nucleic acid molecules of the invention. Preferably, these cells are prokaryotic or eukaryotic cells, for example mammalian cells, bacterial cells, insect cells or yeast cells. The host cells of the invention are preferably characterized by the fact that the introduced nucleic acid molecule of the invention either is heterologous with regard to the transformed cell, i.e. that it does not naturally occur in these cells, or is localized at a place in the genome different from that of the corresponding naturally occurring sequence.

A further embodiment of the invention relates to isolated proteins exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b and being encoded by the nucleic acid molecules of the invention, as well as to methods for their production, whereby, e.g., a host cell of the invention is cultivated under conditions allowing the synthesis of the protein and the protein is subsequently isolated from the cultivated cells and/or the culture medium. Isolation and purification of the recombinantly produced proteins may be carried out by conventional means including preparative chromatography and affinity and immunological separations involving affinity with an anti-Trp8a-, anti-Trp8b-, anti-Trp9-,anti-Trp10a- or anti-Trp10b-antibody, respectively.

As used herein, the term "isolated protein, includes proteins substantially free of other proteins, nucleic acids, lipids, carbohydrates or other materials with which it is naturally associated. Such proteins however not only comprise recombinantly produced proteins but include isolated naturally occurring proteins, synthetically produced proteins, or proteins

produced by a combination of these methods. Means for preparing such proteins are well understood in the art. The Trp proteins are preferably in a substantially purified form. A recombinantly produced version of a human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b protein, including the secreted protein, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67; 31-40 (1988).

In a further preferred embodiment, the present invention relates to an antisense RNA sequence characterised that it is complementary to an mRNA transcribed from a nucleic acid molecule of the present invention or a part thereof and can selectively bind to said mRNA, said sequence being capable of inhibiting the synthesis of the protein encoded by said nucleic acid molecules, and a ribozyme characterised in that it is complementary to an mRNA transcribed from a nucleic acid molecule of the present invention or a part thereof and can selectively bind to and cleave said mRNA, thus inhibiting the synthesis of the proteins encoded by said nucleic acid molecules. Riboyzmes which are composed of a single RNA chain are RNA enzymes, i.e. catalytic RNAs, which can intermolecularly cleave a target RNA, for example the mRNA transcribed from one of the Trp genes. It is now possible to construct ribozymes which are able to cleave the target RNA at a specific site by following the strategies described in the literature. (see, e.g., Tanner et al., in: Antisense Research and Applications, CRC Press Inc. (1993), 415-426). The two main requirements for such ribozymes are the catalytic domain and regions which are complementary to the target RNA and which allow them to bind to its substrate, which is a prerequisite for cleavage. Said complementary sequences, i.e., the antisense RNA or ribozyme, are useful for repression of Trp8a-, Trp8b, Trp9-, Trp10a- and Trp10b-expression, respectively, i.e. in the case of the treatment of a prostate cancer or endometrial cancer (carcinoma of the uterus). Preferably, the antisense RNA and ribozyme of the invention are complementary to the coding region. The person skilled in the art provided with the sequences of the nucleic acid molecules of the present invention will be in a position to produce and utilise the above described antisense RNAs or ribozymes. The region of the antisense RNA and ribozyme, respectively, which shows complementarity to the mRNA transcribed from the nucleic acid molecules of the present invention preferably has a length of at least 10, in particular of at least 15 and particularly preferred of at least 50 nucleotides.

In still a further embodiment, the present invention relates to inhibitors of Trp8a, Trp8b, Trp9, Trp10a and Trp10b, respectively, which fulfill a similar purpose as the antisense RNAs or

ribozymes mentioned above, i.e. reduction or elimination of biologically active Trp8a, Trp8b, Trp9, Trp10a or Trp10b molecules. Such inhibitors can be, for instance, structural analogues of the corresponding protein that act as antagonists. In addition, such inhibitors comprise molecules identified by the use of the recombinantly produced proteins, e.g. the recombinantly produces protein can be used to screen for and identify inhibitors, for example, by exploiting the capability of potential inhibitors to bind to the protein under appropriate conditions. The inhibitors can, for example, be identified by preparing a test mixture wherein the inhibitor candidate is incubated with Trp8a, Trp8b, Trp9, Trp10a or Trp10b, respectively, under appropriate conditions that allow Trp8a, Trp8b, Trp9, Trp10a or Trp10b to be in a native conformation. Such an in vitro test system can be established according to methods well known in the art. Inhibitors can be identified, for example, by first screening for either synthetic or naturally occurring molecules that bind to the recombinantly produced Trp protein and then, in a second step, by testing those selected molecules in cellular assays for inhibition of the Trp protein, as reflected by inhibition of at least one of the biological activities as described in the examples, below. Such screening for molecules that bind Trp8a, Trp8b, Trp9, Trp10a or Trp10b could easily performed on a large scale, e.g. by screening candidate molecules from libraries of synthetic and/or natural molecules. Such an inhibitor is, e.g., a synthetic organic chemical, a natural fermentation product, a substance extracted from a microorganism, plant or animal, or a peptide. Additional examples of inhibitors are specific antibodies, preferably monoclonal antibodies. Moreover, the nucleic sequences of the invention and the encoded proteins can be used to identify further factors involved in tumor development and progression. In this context it should be emphasized that the modulation of the calcium channel of a member of the trp family can result in the stimulation of the immune response of T lymphocytes leading to proliferation of the T lymphocytes. The proteins of the invention can, e.g., be used to identify further (unrelated) proteins which are associated with the tumor using screening methods based on protein/protein interactions, e.g. the two-hybridsystem Fields, S. and Song, O. (1989) Nature (340): 245-246.

The present invention also provides a method for diagnosing a prostate carcinoma which comprises contacting a target sample suspected to contain the protein Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA with a reagent which reacts with Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA and detecting Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA.

It has been found that carcinoma cells of placenta (chorion carcinoma), lung and prostate express Trp10 transcripts as well as Trp10 antisense transcripts and transcripts being in part complementary to Trp10 antisense transcripts. Accordingly, the present invention also provides a method for diagnosing a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense RNA.

When the target is mRNA (or antisense RNA), the reagent is typically a nucleic acid probe or a primer for PCR. The person skilled in the art is in a position to design suitable nucleic acids probes based on the information as regards the nucleotide sequence of Trp8a, Trp8b, Trp10a or Trp10b as depicted in figure 7, 8a, 10 and 11, respectively, or tables 1 and 2, above. When the target is the protein, the reagent is typically an antibody probe. The term "antibody", preferably, relates to antibodies which consist essentially of pooled monoclonal antibodies with different epitopic specifities, as well as distinct monoclonal antibody preparations. Monoclonal antibodies are made from an antigen containing fragments of the proteins of the invention by methods well known to those skilled in the art (see, e.g., Köhler et al., Nature 256 (1975), 495). As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab') 2 fragments) which are capable of specifically binding to protein. Fab and f(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24: 316-325 (1983)). Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimerical, single chain, and humanized antibodies. The target cellular component, i.e. Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts, e.g., in biological fluids or tissues, may be detected directly in situ, e.g. by in situ hybridization (e.g., according to the examples, below) or it may be isolated from other cell components by common methods known to those skilled in the art before contacting with a probe. Detection methods include Northern blot analysis, RNase protection, in situ methods, e.g. in situ hybridization, in vitro amplification methods (PCR, LCR, QRNA replicase or RNA-transcription/amplification (TAS, 3SR), reverse dot blot disclosed in EP-B1 O 237 362)), immunoassays, Western blot and other detection assays that are known to those skilled in the art.

Products obtained by in vitro amplification can be detected according to established methods, e.g. by separating the products on agarose gels and by subsequent staining with ethidium bromide. Alternatively, the amplified products can be detected by using labeled primers for amplification or labeled dNTPs.

The probes can be detectable labeled, for example, with a radioisotope, a bioluminescent, compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

Expression of Trp8a, Trp8b, Trp10a and Trp10b, respectively, in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101 (1985), 976-985; Jalkanen et al., J. Cell. Biol. 105 (1987), 3087-3096; Sobol et al. Clin. Immunpathol. 24 (1982), 139-144; Sobol et al., Cancer 65 (1985), 2005-2010). Other antibody based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium rhodamine, and biotin. In addition to assaying Trp8a, Trp8b, Trp 10a or Trp10b levels in a biological sample, the protein can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by Xradiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ¹³¹I, ¹¹²In, ⁹⁹mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99 mTc. The labeled antibody or antibody fragment will then preferentially accumulate at he location of cells which contain the specific protein. In

vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments". (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B.A. Rhodes, eds., Masson Publishing Inc. (1982)).

The marker Trp8a and Trp8b is also useful for prognosis, for monitoring the progression of the tumor and the diagnostic evaluation of the degree of malignancy of a prostate tumor (grading and staging), e.g. by using in situ hybridization: In a primary carcinoma Trp8 is expressed in about 2 to 10% of carcinoma cells, in a rezidive carcinoma in about 10 to 60% of cells and in metastases in about 60 to 90% of cells.

The present invention also relates to a method for diagnosing endometrial cancer (cancer of the uterus) which comprises contacting a target sample suspected to contain the protein Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA with a reagent which reacts with Trp8a and/or Trp8b or the encoding mRNA and detecting Trp8a and/or Trp8b encoding mRNA. As regards particular embodiments of this method reference is made to the particular embodiments of the method of diagnosing a prostate cancer outlined above.

For evaluating whether the concentration of Trp8a, Trp8b, Trp10a or Trp10b or the concentration of Trp8a, Trp8b, Trp10a or Trp10b encoding mRNA is normal or increased, thus indicative for the presence of a malignant tumor, the measured concentration is compared with the concentration in a normal tissue, preferably by using the ratio of Trp8a:Trp9, Trp8b:Trp9 or Trp10(a or b)/Trp9 for quantification.

Since the prostate carcinoma forms its own basement membrane when growing invasively, it can be concluded that only cells expressing Trp8 and Trp10 are involved in this phenomenon. Thus, it can be concluded that by inhibiting the expression and/or activity of these proteins an effective therapy of cancers like PCA is provided.

Thus, the present invention also relates to a pharmaceutical composition containing a reagent which decreases or inhibits Trp8a, Trp8b, Trp10a and/or Trp10b expression or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b, and a method for preventing, treating, or ameliorating a prostate tumor, endometrial cancer (uterine carcinoma) tumor, a chorion carcinoma, cancer of the lung or melanoma, which comprises administering to a mammalian subject a

therapeutically effective amount of a reagent which decreases or inhibits Trp8a, Trp8b, Trp10a and/or Trp10b expression or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b. Examples of such reagents are the above described antisense RNAs, ribozymes or inhibitors, e.g. specific antibodies. Furthermore, peptides, which inhibit or modulate the biological function of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b may be useful as therapeutical reagents. For example, these peptides can be obtained by screening combina torial phage display libraries (Cosmix, Braunschweig, Germany) as described by Rottgen, P. and Collins, J. (Gene (1995) 164 (2): 243-250). Furthermore, antigenic epitopes of the Trp8 and Trp10 proteins can be identified by the expression of recombinant Trp8 and Trp10 epitope libraries in E. coli (Marquart, A. & Flockerzi, V., FEBS Lett. 407 (1997), 137-140; Trost, C., et al., FEBS Lett. 451 (1999) 257-263 and the consecutive screening of these libraries with serum of patients with cancer of the prostate or of the endometrium. Those Trp8 and Trp10 epitopes which are immunogenic and which lead to the formation of antibodies in the serum of the patients can be then be used as Trp8 or Trp10 derived peptide vaccines for immune inventions against cancer cells which express Trp8 or Trp10. Alternatively to the E. coli expression system, Trp8 or Trp10 or epitopes of Trp8 and Trp10 can be expressed in mammalian cell lines such as human embryonic kidney (Hek 293) cells (American Type Culture Collection, ATCC CRL 1573).

Finally, compounds useful for therapy of the above described diseases comprise compounds which act as antagonists or agonists on the ion channels Trp8, Trp9 and Trp10. It could be shown that Trp8 is a highly calcium selective ion channel which in the presence of monovalent (namely sodium) and divalent ions (namely calcium) is only permeable for calcium ions (see Example 4, below, and Figures 3A, C, E). Under physiological conditions, Trp8 is a calcium selective channel exhibiting large inward currents. This very large conductance of Trp8 channels (as wells as Trp9 and Trp10a/b channels) is useful to establish systems for screening pharmacological compounds interacting with Trp-channels including high throughput screening systems. Useful high throughput screening systems are well known to the person skilled in the art and include, e.g., the use of cell lines stably or transiently transfected with DNA sequences encoding Trp8, Trp9 and Trp10 channels in assays to detect calcium signaling in biological systems. Such systems include assays based on Ca-sensitive dves such as aequorin, apoaequorin, Fura-2, Fluo-3 and Indo-1.

Accordingly, the present invention also relates to a method for identifying compounds which act as agonists or antagonists on the ion channels Trp8, Trp9 and/or Trp10, said method comprising contacting a test compound with the ion channel Trp8, Trp9 and/or Trp10, preferably by using a system based on cells stably or transiently transfected with DNA sequences encoding Trp8, Trp9 and/or Trp10, and determining whether said test compound affects the calcium uptake.

For administration the above described reagents are preferably combined with suitable pharmaceutical carriers. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Such carriers can be formulated by conventional methods and can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g. by intraperetoneal. subcutaneous. intramuscular, topical intradermal intravenous, or administration. The route of administration, of course, depends on the nature of the tumor and the kind of compound contained in the pharmaceutical composition. The dosage regimen will be determined by the attending physician and other clinical factors. As is well known in the medical arts, dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind and stage of the tumor, general health and other drugs being administered concurrently.

The delivery of the antisense RNAs or ribozymes of the invention can be achieved by direct application or, preferably, by using a recombinant expression vector such as a chimeric virus containing these compounds or a colloidal dispersion system. By delivering these nucleic acids to the desired target, the intracellular expression of Trp8a, Trp8b, Trp10a and/or Trp10b and, thus, the level of Trp8a, Trp8b, Trp10a and/or Trp10b can be decreased resulting in the inhibition of the negative effects of Trp8a, Trp8b, Trp10a and/or Trp10b, e.g. as regards the metastasis formation of PCA.

Direct application to the target site can be performed, e.g., by ballistic delivery, as a colloidal dispersion system or by catheter to a site in artery. The colloidal dispersion systems which can be used for delivery of the above nucleic, acids include macromolecule complexes, nanocapsules, microspheres, beads and lipid-based systems including oil-in-water emulsions

(mixed), micelles, liposomes and lipoplexes, The preferred colloidal system is a liposome. The composition of the liposome is usually a combination of phospholipids and steroids, especially cholesterol. The skilled person is in a position to select such liposomes which are suitable for the delivery of the desired nucleic acid molecule. Organ-specific or cell-specific liposomes can be used in order to achieve delivery only to the desired tumor. The targeting of liposomes can be carried out by the person skilled in the art by applying commonly known methods. This targeting includes passive targeting (utilizing the natural tendency of the liposomes to distribute to cells of the RES in organs which contain sinusoidal capillaries) or active targeting (for example by coupling the liposome to a specific ligand, e.g., an antibody, a receptor, sugar, glycolipid, protein etc., by well known methods). In the present invention monoclonal antibodies are preferably used to target liposomes to specific tumors via specific cell-surface ligands.

Preferred recombinant vectors useful for gene therapy are viral vectors, e.g. adenovirus, herpes virus, vaccinia, or, more preferably, an RNA virus such as a Retrovirus. Even more preferably, the retroviral vector is a derivative of a murine or avian retrovirus. Examples of such retroviral vectors which can be used in the present invention are: Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV) and Rous sarcoma virus (RSV). Most preferably, a non-human primate retroviral vector is employed, such as the gibbon ape leukemia virus (GaLV), providing a broader host range compared to murine vectors. Since recombinant retroviruses are defective, assistance is required in order to produce infectious particles. Such assistance can be provided, e.g., by using helper cell lines that contain plasmids encoding all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR. Suitable helper cell lines are well known to those skilled in the art. Said vectors can additionally contain a gene encoding a selectable marker so that the transduced cells can be identified. Moreover, the retroviral vectors can be modified in such a way that they become target specific. This can be achieved, e.g., by inserting a polynucleotide encoding a sugar, a glycolipid, or a protein, preferably an antibody. Those skilled in the art know additional methods for generating target specific vectors. Further suitable vectors and methods for in vitro- or in vivo-gene therapy are described in the literature and are known to the persons skilled in the art; see, e.g., WO 94/29469 or WO 97/00957.

In order to achieve expression only in the target organ, i.e. tumor to be treated, the nucleic acids encoding, e.g. an antisense RNA or ribozyme can also be operably linked to a tissue specific promoter and used for gene therapy. Such promoters are well known to those skilled in the art (see e.g. Zimmermann et al., (1994) Neuron 12, 11-24; Vidal et al.; (1990) EMBO J. 9, 833-840; Mayford et al., (1995), Cell 81, 891-904; Pinkert et al., (1987) Genes & Dev. 1, 268-76).

For use in the diagnostic research discussed above, kits are also provided by the present invention. Such kits are useful for the detection of a target cellular component, which is Trp8a, Trp8b, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts, wherein the presence or an increased concentration of Trp8a, Trp8b, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts is indicative for a prostate tumor, endometrial cancer, melanoma, chorion carcinoma or cancer of the lung, said kit comprising a probe for detection of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts. The probe can be detectably labeled. Such probe may be a specific antibody or specific oligonucleotide. In a preferred embodiment, said kit contains an anti-Trp8a-, anti-Trp8b-, anti-Trp9-, anti-Trp10a-and/or anti-Trp10b-antibody and allows said diagnosis, e.g., by ELISA and contains the antibody bound to a solid support, for example, a polystyrene microtiter dish or nitrocellulose paper, using techniques known in the art. Alternatively, said kits are based on a RIA and contain said antibody marked with a radioactive isotope. In a preferred embodiment of the kit of the invention the antibody is labeled with enzymes, fluorescent compounds, luminescent compounds, ferromagnetic probes or radioactive compounds. The kit of the invention may comprise one or more containers filled with, for example, one or more probes of the invention. Associated with container (s) of the kit can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, us or sale for human administration.

EXAMPLES

The following Examples are intended to illustrate, but not to limit the invention. While such Examples are typical of those that might be used, other methods known to those skilled in the art may alternatively be utilized.

Example 1: Materials and Methods

(A) Isolation of cDNA clones and Northern blot analysis

Total RNA was isolated from human placenta an prostate using standard techniques. Isolation of mRNA was performed with poly (A)⁺RNA - spin columns (New England Biolabs, Beverly, USA) according to the instructions of the manufacturer. Poly (a) ⁺RNA was reverse transcribed using the cDNA choice system (Gibco-BRL, Rockville, USA) and subcloned in λ-Zap phages (Stratagene, La Jolla, USA). An human expressed sequence tag (GenBank accession number 1404042) was used to screen an oligo d(T) primed human placenta cDNA library. Several cDNA clones were identified and isolated. Additional cDNA clones were isolated from two specifically primed cDNA libraries using primers 5'-gca tag gaa ggg aca ggt gg-3' and 5'-gag agt cga ggt cag tgg tcc-3'.

cDNA clones were sequenced using a thermocycler (PE Applied Biosystems, USA) and Thermo Sequenase (Amersham Pharmacia Biotech Europe, Freiburg, Germany). DNA sequences were analyzed with an automated sequencer (Licor, Linccoln, USA).

For Northern blot analysis 5 µg human poly (A)⁺ RNA from human placenta or prostate were separated by electrophoresis on 0.8 % agarose gels. Poly (A)⁺ RNA was transferred to Hybond N nylon membranes (Amersham Pharmacia Biotech Europe, Freiburg, Germany). The membranes were hyridized in the presence of 50 % formamide at 42° C over night. DNA probes were labelled using [α^{32} P]dCTP and the "ready prime, labelling kit (Amersham Pharmacia Biotech Europe, Freiburg, Germany). Commercial Northern blots were hybridized according to the distributors instructions (Clontech, Paolo Alto, USA).

(B) Construction of expression plasmids and transfection of HEK 293 cells

Lipofections were carried out with the recombinant dicistronic eucaryotic expression plasmid pdiTRP8 containing the cDNA of Trp8b under the control of the chicken ß-actin promotor followed by an internal ribosome entry side (IRES) and the cDNA of the green fluorescent protein (GFP). To obtain pdiTRP8 carrying the entire protein coding regions of TRP8b and

the GFP (Prasher, D.C. et al. (1992), Gene 111, 229-233), the 5'and 3'-untranslated sequences of the TRP8b cDNA were removed, the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was introduced immediately 5'of the translation initiation codon and the resulting cDNA was subcloned into the pCAGGS vector (Niwa, H., Yamamura, K. and Miyazaki, J (1991), Gene 8, 193-199) downstream of the chicken β-actin promotor. The IRES derived from encephalmyocarditis virus (Kim, D.G., Kang, H.M., Jang, S.K. and Shin H.S. (1992) Mol.Cell.Biol. 12, 3636-3643) followed by the GFP cDNA containing a Ser65Thr mutation (Heim, R., Cubitt, A.B., Tsien, R.Y. (1995) Nature 373, 663-664) was then cloned 3' to the TRP8b cDNA. The IRES sequence allows the simultaneous translation of TRP8b and GFP from one transcript. Thus, transfected cells can be detected unequivocally by the development of green fluorescence.

For monitoring of the intracellular Ca²⁺ concentration human embryonic kidney (HEK 293) cells were cotransfected with the pcDNA3-TRP8b vector and the pcDNA3-GFPvector in a molar ratio of 4:1 in the presence of lipofectamine (Quiagen, Hilden, Germany). To obtain pcDNA3-TRP8b the entire protein coding region of TRP8b including the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was subcloned into the pcDNA3 vector (Invitrogen, Groningen, Netherlands). Calcium monitoring and patch clamp experiments were carried out two days and one day after transfection, respectively.

(C) Chromosomal localization of the Trp8 gene

The chromosomal localization of the human TRP8 gene was performed using NIGMS somatic hybrid mapping panel No.2 (Coriell Institute, Camden, NJ, USA) previously described (Drwinga, H.L., Toji, L.H., Kim, C.H., Greene, A.E., Mulivor, R.A. (1993) Genomics 16, 311-314; Dubois, B.L. and Naylor, S.L. (1993) Genomics 16, 315-319).

(D) In Vitro Translation, glutathione - sepharose and calmodulin agarose binding assay N- and C-terminal Trp8-fragments were subcloned into the pGEX-4T2 vector (Amersham Pharmacia Europe, Freiburg, Germany) resulting in glutathione-S-transferase (GST)-Trp8 fusion constructs (Fig. 4). The GST-TRP8-fusion proteins were expressed in E. coli BL 21 cells and purified using glutathione - sepharose beads (Amersham Pharmacia Biotech Europe, Freiburg, Germany).

In vitro translation of human Trp8 cDNA and Xenopus laevis calmodulin cDNA (Davis, T.N. and Thorner, J. Proc.Natl.Acad.Sci. USA 86, 7909-7913.) was performed in the presence of ³⁵S-methionine using the TNT coupled transcription/translation kit (Promega, Madison, USA). Translation products were purified by gel fliltration (Sephadex G50, Amersham Pharmacia Biotech Europe, Freiburg, Germany) and equal amounts of ³⁵S labeled probes were incubated for 2 h with glutathione beads bound to GST - Trp8 or calmodulin - agarose (Calbiochem) in 50 mM Tris-HCl, pH 7.4, 0.1 % Triton X-100, 150 mM NaCl in the presence of 1 mM Ca²⁺ or 2 mM EGTA. After three washes, bound proteins were eluted with SDS sample buffer, fractionated by SDS-PAGE and ³⁵S labeled proteins were detected using a Phosphor Imager (Fujifilm, Tokyo, Japan).

(E) Calcium measurements

The intracellular Ca²⁺ concentration ([Ca²⁺]_i) was determined by dual wavelength fura-2 fluorescence ratio measurements (Tsien, R.Y. (1988) Trends Neurosci. 11, 419-424) using a digital imaging system (T.I.L.L. Photonics, Planegg, Germany). HEK cells were grown in minimal essential medium in the presence of 10 % fetal calf serum and cotransfected with the pcDNA3-TRP8b vector and the pcDNA3-GFPvector as described above (B). Transfected cells were detected by development of green fluorescence. The cells were loaded with 4μM fura-2/AM (Molecular Probes, Oregon, USA) for one hour. After loading the cells were rinsed 3 times with buffer B1 (10 mM Hepes, 115 mM NaCl, 2 mM MgCl₂, 5mM KCl, pH 7.4) and the [Ca²⁺]_i was calculated from the fluorescence ratios obtained at 340 and 380 nm excitation wavelengths as described (Garcia, D.E., Cavalié, A. and Lux, H.D. (1994) J. Neurosci 14, 545-553).

(F) Electrophysiological recordings

HEK cells were transfected with the eucaryotic expression plasmid pdiTRP8 described in (B) and electrophysiological recordings were carried out one day after transfection. Single cells were voltage clamped in the whole cell mode of the patch clamp technique as described (Hamill, O.P., Marty, A., Neher, E., Sakmann, B. and Sigworth, F.J. (1981) Pflügers Arch. 391, 85-100; Philipp, S., Cavalié, A., Freichel, M., Wissenbach, U., Zimmer, S., Trost, C., Marquart, A., Murakami, M. and Flockerzi, V. (1996) EMBO J. 6166-6171). The pipette solution contained contained (mM): 140 aspartic acid, 10 EGTA, 10 NaCl, 1 MgCl2, 10 Hepes (pH 7.2 with CsOH) or 125 CsCl, 10 EGTA, 4 CaCl₂ 10 Hepes (pH 7,2 with CsOH). The bath solution contained (mM): 100 NaCl, 10 CsCl, 2 MgCl₂, 50 mannitol, 10 glucose, 20

Hepes (pH 7,4 with CsOH) and 2 CaCl₂, or no added CaCl₂ (-Ca²⁺ solution). Divalent free bath solution contained (mM): 110 N-methyl-D-glucamine (NMDG). Whole cell currents were recorded during 100 msec voltage ramps from -100 to +100 mV at varying holding potentials.

(G) In Situ Hybridization

In situ hybridizations were carried out using formalin fixed tissue slices of 6 - 8 µM thickness. The slices were hydrated and incubated in the presence of PBS buffer including 10 µg / ml proteinase K (Roche Diagnostics, Mannheim, Germany) for 0.5 h. The slices were hybridized at 37°C using biotinylated deoxy-oligonucleotides (0.5 pmol / µl) in the presence of 33 % formamide for 12 h. Furthermore the slices were several times rinsed with 2 x SSC and incubated at 25°C for 0.5 h with avidin / biotinylated horse raddish peroxidase complex (ABC, DAKO, Santa Barbara, USA). After several washes with PBS buffer the slices were incubated in the presence of biotinylated tyramid and peroxide (0.15 % w/v) for 10 min. rinsed with PBS buffer and additionally incubated with ABC complex for 0.5 h. The slices were washed with PBS buffer and incubated in the presence of DAB solution (diaminobenzidine (50µg / ml), 50 mM Tris/EDTA buffer pH 8.4, 0.15 % H₂O₂ in N,N dimethyl-formamide; Merck, Darmstadt, Germany), The detection was stopped after 4 minutes by incubating the slides in water. Tyramid was biotinylated by incubating NHS-LC Biotin (sulfosuccinimidyl-6-(biotinimid)-hexanoat), 2.5 mg/ml; Pierce, Rockford, USA) and tyramin-HCl (0.75 mg / ml, Sigma) in 25 mM borate buffer pH 8.5 for 12 h. The tyramid solution was diluted 1 - 5: 1000 in PBS buffer.

(H) GenBank accession numbers: TRP8a, Aj243500; TRP8b Aj243501

Example 2: Expression of TRP8 transcripts

In search of proteins distantly related to the TRP family of ion channels, an human expressed sequence tag (EST, GenBank accession number 1404042) was identified in the GenBank database using BLAST programms (at the National Center for Biotechnology Information (NCBI); Altschul, S.F., Gish, W., Miller, W., Myers, E.W. and Lipman, D.J.J. (1990) Mol. Biol. 5, 403-410) being slightly homologous to the VR1 gene. Several human placenta cDNA libraries were constructed and screeened with this EST DNA as probe. Several full length

cDNA clones were identified and isolated. The full length cDNA clones encoded two putative proteins differing in three amino acids and were termed Trp8a and Trp8b (Fig. 1c, 2a, 7 and 8A). This finding was reproduced by isolating cDNA clones from two cDNA libraries constructed from two individual placentas. The derived protein sequence(s) comprises six transmembrane domains, a characteristic overall feature of trp channels and related proteins (Fig.: 1b). The sequence is closely related to the meanwhile published calcium uptake transport protein 1 (CaT1), isolated from rat intestine (Peng, J.B., Chen, X.Z., Berger, U.V., Vassilev, P.M., Tsukaguchi, H., Brown, E.M. and Hediger M.A. (1999) J Biol Chem. 6;274, 22739-22746) and to the epithelial calcium uptake channel (ECaC) isolated from rabbit kidney (Hoenderop, J.G., van der Kemp, A.W., Hartog, A., van de Graaf, S.F., van Os, C.H., Willems, P.H. and Bindels, R.J. (1999) J Biol Chem. 26;274, 8375-8378). Expression of Trp8a/b transcripts are detectable in human placenta, pancreas and prostate (Fig.: 5) and the size of the Northern signal (3.0 kb) corresponds with the size of the isolated full length cDNAs. In addition, a shorter transcript of 1.8 kb, probably a splice variant, is detectable in human testis. The Trp8 mRNA is not expressed in small intestine or colon (Fig.: 5) implicating that Trp8 is not the human ortholog of the rat CaT1 or rabbit ECaC proteins. To investigate whether there are other related sequences Trp8a/b derived primers (UW241, 5'-TAT GAG GGT TCA GAC TGC-3' and UW242, 5'-CAA AGT AGA TGA GGT TGC-3') were used to amplify a 105 bp fragment from human genomic DNA being 95% identical on the nucleotide level to the Trp8 sequence (data not shown). This indicates the existence of several similar sequences in humans at least at the genomic level.

Example 3: Two variants of the Trp8 protein (Trp8a and Trp8b) arise by polymorphism

Two variants of the Trp8 cDNA were isolated from human placenta (Fig.: 2A, 7 and 8A) which encoded two proteins which differ in three amino acids and were termed Trp8a and Trp8b. Trp8a/b specific primers were designed to amplify a DNA fragment of 458 bp of the Trp8 gene from genomic DNA isolated from human T-lymphocytes (primer pair: UW243, 5'-CAC CAT GTG CTG CAT CTA CC-3' and UW244, 5'-CAA TGA CAG TCA CCA GCT CC-3'). The amplification product contains a part of the sequence where the derived protein sequence of Trp8a comprises the amino acid valine and the Trp8b sequence methionine as well as a silent base pair exchange (g versus a) and an intron of 303bp (Fig.: 2.A, B). Both variants of the Trp8 genes (a,b) were amplified from genomic DNA in equal amounts indicating the existence of both variants in the human genome and therefore being not the

result of RNA editing (Fig.: 2B). The Trp8a gene can be distinguished from the Trp8b gene by cutting the genomic fragment of 458bp with the restriction enzyme Bsp1286I (Fig. 2B). Using human genomic DNA isolated from blood of twelve human subjects as template, the 458bp fragment was amplified and restricted with BSP1286I. In eleven of the tested subjects only the Trp8b gene is detectable, while one subject (7) contains Trp8a and Trp8b genes (Fig.: 2D). These implicates that the two Trp8 variants arise by polymorphism and do not represent individual genes. Using Trp8 specific primers and chromosomal DNA as template, the Trp8 locus is detectable on chromosome 7 (Fig.: 2C).

Example 4: Trp8b is a calcium permeable channel

The protein coding sequence of the Trp8b cDNA was subcloned into pcDNA3 vector (Invitrogen, Groningen, Netherlands) under the control of the cytomegalovirus promotor (CMV). Human embryonic kidney (HEK 293) cells were cotransfected with the Trp8b pcDNA3 construct (pcDNA3-Trp8b vector) and the pcDNA3-GFPvector encoding the green fluorescent protein (GFP) in 4:1 ratio. The Trp8b cDNA and the cDNA of the reporter, GFP, was transiently expressed in human embryonic kidney (HEK 293) cells. The intracellular Ca²⁺ concentration ([Ca²⁺]_i) and changes of [Ca²⁺]_i were determined by dual wavelength fura-2 fluorescence ratio measurements (Fig.: 3F) in cotransfected cells which were identified by the green fluorescence of the reporter gene GFP.

Dual wavelength fura-2 fluorescence ratio measurement is a standard procedure (e.g. in: An introduction of Molecular Neurobiology (ed. Hall, Z.W.)Sinauer Associates, Sunderland, USA (1992)) using fura-2, which is a fluorescent Ca²⁺ sensitive dye and which was designed by R.Y.Tsien (e.g. Trends Neurosci. 11, 419-424 (1988) based upon the structure of EGTA. Its fluorescence emission spectrum is altered by binding to Ca²⁺ in the physiological concentration range. In the absence of Ca²⁺, fura-2 fluoresces most strongly at an excitation wavelength of 385 nm; when it binds Ca²⁺, the most effective excitation wavelength shifts to 345 nm. This property is used to measure local Ca²⁺ concentrations within cells. Cells can be loaded with fura-2 esters (e.g. fura-2AM) that diffuse across cell membranes and are hydrolyzed to active fura-2 by cytosolic esterases.

In the presence of 1mM Ca²⁺, Trp8 expressing cells typically contained more than 300 nM cytosolic Ca²⁺, while non transfected controls contained less than 100 nM Ca²⁺ ions (Fig. 3F).

When Trp8b transfected cells were incubated without extracellular Ca²⁺, the intracellular Ca²⁺ concentration ([Ca²⁺]_i) decreased to levels comparable to non transfected cells. Readdition of 1mM Ca²⁺ to the bath resulted in significant increase of the cytosolic [Ca²⁺] in Trp8b transfected cells, but not in controls (Fig.: 3F). After readdition of Ca²⁺ ions to the bath solution, the cytosolic Ca²⁺ concentration remains on a high steady state level in the Trp8b transfected cells.

Example 5: Trp8 expressing cells show calcium selective inward currents

To characterize in detail the electrophysiological properties of TRP8, TRP8 and GFP were coexpressed in HEK293 cells using the dicistronic expression vector pdiTRP8 and measured currents using the patch clamp technique in the whole cell mode (Hamill, O.P., Marty, A., Neher, E., Sakmann, B. and Sigworth, F.J. (1981) Pflugers Arch., 391, 85-100).

The eucaryotic expression plasmid pdiTRP8 contains the cDNA of Trp8b under the control of the chicken β-actin promotor followed by an internal ribosome entry side (IRES) and the cDNA of the green fluorescent protein (GFP). To obtain pdiTRP8 carrying the entire protein coding regions of TRP8b and the GFP (Prasher, D.C. et al. (1992), Gene 111, 229-233), the 5'and 3'-untranslated sequences of the TRP8b cDNA were removed, the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was introduced immediately 5'of the translation initiation codon and the resulting cDNA was subcloned into the pCAGGS vector (Niwa, H., Yamamura, K. and Miyazaki, J (1991), Gene 8, 193-199) downstream of the chicken β-actin promotor. The IRES derived from encephalmyocarditis virus (Kim, D.G., Kang, H.M., Jang, S.K. and Shin H.S. (1992) Mol.Cell.Biol. 12, 3636-3643) followed by the GFP cDNA containing a Ser65Thr mutation (Heim, R., Cubitt, A.B., Tsien, R.Y. (1995) Nature 373, 663-664) was then cloned 3' to the TRP8b cDNA. The IRES sequence allows the simultaneous translation of TRP8b and GFP from one transcript. Thus, transfected cells can be detected unequivocally by the development of green fluorescence.

In the presence of 2 mM external calcium, Trp8b transfected HEK cells show inwardly rectifying currents, the size of which depends on the level of intracellular calcium and the electrochemical driving force. The resting membrane potential was held either at -40 mV, or, to lower the driving force for calcium influx in between pulses, at +70 mV. Current traces

were recorded in response to voltage ramps from -100 to +100 mV, that were applied every second. To monitor inward and outward currents over time, we analyzed the current size at -80 and + 80 mV of the ramps. Figure 3A shows a representative trace of the current at -80mV over time. Both at a holding potential of -40 mV or at +70 mV, the currents are significantly larger than in cells transfected with only the GFP containing vector (Fig.: 3E). Interestingly, after changing to a positive holding potential, current size in Trp8 transfected cells slowly increases and reaches steady state after approximately 70 seconds (Fig.: 3A). To determine the selectivity of the induced currents, we then perfused the cells with solutions that either contain no sodium, no added Ca²⁺ (Fig. 3A, C) or a sodium containing, but divalent ion free bath solution. To control for the effect of the solution change alone, we also perfused with normal bath (see puff in Fig. 3A). While removal of external Ca²⁺ completely abolishes the trp 8 induced currents - the remaining current being identical in size and shape to the control (Fig.: 3A, C, E), removal of external sodium has no effect (Fig.: 3E). An important hallmark of calcium selective channels (e.g. Vennekens, R., Hoenderop, G.J., Prenen, J., Stuiover, M., Willems, PHGM, Droogmans, G., Nilius, B. and Bindels, R.J.M (1999) J. Biol. Chem. 275, 3963-3969), is their ability to conduct sodium only if all external divalent ions, namely Ca²⁺ and magnesium are removed. To test whether the trp 8 channel conforms with this phenomenon normal bath solution was switched to a solution containing only sodium and 1 mM EGTA. As can be seen in Figure 3B and D, Trp8 transfected cells can now conduct very large sodium currents. Interestingly, immediately after the solution change, the currents first become smaller before increasing rapidly, indicating that the pore may initially still be blocked by calcium a phenomenon usually called anomalous mole fraction behaviour (Warnat, J., Philipp, S., Zimmer, S., Flockerzi, V., and Cavalié A. (1999) J. Physiol. (Lond) 518, 631-638). The measured outward currents of Trp8 transfected cells in normal bath solution are not significantly different from non-transfected control cells or cells which only express the reporter gene GFP. As the removal of external Ca2+ abolishes the Trp8 specific current, the remaining current was subtracted from the current before the solution change to obtain the uncontaminated Trp8 conductance (see inset in Fig.: 3C). As expected from the given ionic conditions (high EGTA inside, 2 mM Ca2+ outside), the current-voltage relationship now shows prominent inward rectification with little to no outward current.

Both the time course of the development of Trp8 currents and the size of the currents depend on the frequency of stimulation (data not shown), the internal and external Ca²⁺ concentration

and the resting membrane potential, suggesting that Trp8 calcium conductance is intrically regulated by a Ca²⁺ mediated feedback mechanisms.

Example 6: Ca2+ / calmodulin binds to the C-terminus of the Trp8 protein

To test whether calmodulin, a prime mediator of calcium regulated feedback, is involved, first it was investigated biochemically whether Trp8 protein can bind calmodulin. Trp8 cDNA was in vitro translated in the presence of ³⁵S-methionine and the product incubated with calmodulin-agarose beads. After several washes either in the presence or abscence of Ca²⁺, the beads were incubated in Laemmli buffer and subjected to SDS-polyacrylamide gel electrophoresis. In the presence of Ca²⁺ (1mM), but not in the absence of Ca²⁺, Trp8 protein binds to calmodulin (Fig.: 4B).

To narrow down the binding site, two approaches were undertaken: Firstly, GST-TRP8 fusion proteins of various intracellular domains of Trp8 were constructed, expressed in E. coli and bound to gluthathione sepharose beads. These beads were then incubated with in vitro translated 35S- labeled calmodulin, washed and subjected to gel electrophoresis. Secondly, truncated versions of in vitro translated Trp8 protein were used in the above described binding to calmodulin-agarose. As shown in Figure 4A, and C, fusion proteins of the N-terminal region (N1, N2) of Trp8 did not bind calmodulin, while C-terminal fragments (C1, C2, C3, C4) showed calmodulin binding in the presence of calcium (for localization of fragments within the entire Trp8 protein see Fig. 4C). Accordingly, a truncated version of in vitro translated Trp8, which lacks the C-terminal 32 amino acid residues did not bind to calmodulin-agarose (4B). We have restricted the calmodulin binding site to amino acid residues 691 to 711 of the Trp8 protein. This calmodulin binding site does not resemble the typical conserved IQ - motif of conventional myosins, but has limited sequence homology to the calcium dependent calmodulin binding site 1 of the transient receptor potential like (trpl) protein of Drosophila melanogaster (Warr and Kelly, 1996) with several charged amino acid residues conserved. The sequence of the calmodulin binding site of the Trp8 protein resembles a putative amphipathic α-helical wheel structure with a charged and a hydrophobic site according to a model proposed by Erickson-Vitanen and De Grado (1987, Methods Enzymol. 139, 455-478.).

Example 7: Expression of Trp8 transcripts in human placenta and pancreas

Several slides from a human placenta of a ten week old abort were used for in situ hybridization experiments. The in situ hybridization experiments revealed expression of Trp8 transcripts in human placenta (Fig.: 5B). Expression was detectable in trophoblasts and syncytiotrophoblasts of the placenta, but not in Langhans cells.

Trp8 transcripts are detectable in human pancreas (Fig.: 5A). Therefore Trp8 probes were hybridized to tissue sections of human pancreas. The pancreatic tissues were removed from patients with pancreas cancer. Trp8 expression is detectable in pancreatic acinar cells, but not in Langerhans islets (Fig.: 5C). No Trp8 expression was found in regions of pancreatic carcinomas (data not shown).

Furthermore, the Trp8 cDNA is not detectable in human colon nor in human kidney by in situ hybridization as well as by Northern analysis (Fig.: 5A, D). The Northern results taken together with the in situ expression data indicate that the Trp8 protein is not the human ortholog of the CaT1 and ECaC channels cloned from rat intestine (Peng, J.B., Chen, X.Z., Berger, U.V., Vassilev, P.M., Tsukaguchi, H., Brown, E.M. and Hediger M.A.(1999) J Biol Chem. 6;274, 22739-22746) and from rabbit kidney (Hoenderop, J.G., van der Kemp, A.W., Hartog, A., van de Graaf, S.F., van Os, C.H., Willems, P.H. and Bindels, R.J. (1999) J Biol Chem. 26;274, 8375-8378), respectively. Trp8 is unlikely to represent the human version of CaT1 as its expression is undetectable in the small intestine and colon tissues where CaT1 is abundantly expressed. If, however, Trp8 is the human version of rat CaT1, a second gene product appears to be required for Ca²⁺ uptake in human small intestine and colon attributed to CaT1 in rat small intestine and colon.

Example 8: Differential expression of Trp8 transcripts in benign and malign tissue of the prostate

The Trp8 transcripts are expressed in human prostate as shown by hybridization of a Trp8 probe to a commercial Northern blot (Clontech, Palo Alto, USA) (Fig.: 5A). Trp8 transcripts were not detectable by Northern blot analysis using pooled mRNA of patients with benign prostatic hyperplasia (BPH) (Fig.: 5A, prostate*). To examine Trp8 expression on the cellular

level, sections of prostate tissues were hybridized using Trp8 specific cDNA probes (Table 3). Expression of Trp8 transcripts is not detectable in normal prostate (n = 3), benign hyperplasia (BPH, n = 15) or prostatic intraepithelial neoplasia (PIN, n = 9) (Fig.: 6A, C, E). Trp8 transcripts were only detectable in prostate carcinoma (PCA), although with different expression levels. Low expression levels were found in primary carcinomas (2 - 10 % of the carcinoma cells, n = 8) (Fig.: 7B). Much stronger expression was detectable in rezidive carcinoma (10 - 60 %) (Fig.: 7D, n = 6) and metastases of the prostate (60 - 90 %, n = 4) (Fig.: 7F). Thus it has to be concluded that the commercial Northern blot used in Fig.: 5A contains not only normal prostate mRNA as indicated by the distributor. According to the distributors instructions the prostate mRNA used for this Northern blot was collected from 15 human subjects in the range of 14 to 60 years of age. This prostate tissue was not examined by pathologic means. Since Trp8 expression is not detectable in normal or benign prostate, this finding implicates that the mRNA used for this Northern blot was extracted in part from prostatic carcinoma tissue. To summarize, Trp8 expression is only detectable in malign prostate and, thus, the Trp8 cDNA is a marker for prostate carcinoma. The results are summarized in Table 4.

Table 3

Trp8 probes used for in situ hybridization:

Probes (antisense)

- 1.) 5' TCCGCTGCCGGTTGAGATCTTGCC 3'
- 2.) 5' CTTGCTCCATAGGCAGAGAATTAG 3'
- 3.) 5' ATCCTCAGAGCCCCGGGTGTGGAA3'

Controls (sense)

- 1.) 5' GGCAAGATCTCAACCGGCAGCGGA 3'
- 2.) 5' CTAATTCTCTGCCTATGGAGCAAG 3'
- 3.) 5' TTCCACACCCGGGGCTCTGAGGAT 3'

Table 4

Prostate	total	negative	positive
normal	3	3	0
BPH	15	15	0
PIN	9	9	0

carcinoma 18 1 17

(B) Differential expression of Trp8 transcripts in benign and malign tissue of the uterus

Moreover it could be shown that Trp8 is expressed in endometrial cancer (also called cancer of the uterus, to be distinguished from uterine sarcoma or cancer of the cervix) whereas no expression was observed in normal uterus tissue. Thus, Trp8 also is a specific marker for the diagnosis of the above cancer (Fig. 12).

Example 9: Characterization of Trp9

The complete protein coding sequence of Trp9 was determined (Fig. 9). Trp 9 transcripts are predominantly expressed in the human prostate and in human colon. As it could be shown by Northern blot analysis, there is no difference of the expression of TRP9 in benigne prostata hyperplasia (BPH, Fig. 13, upper panel left) or prostate carcinoma (Fig. 13, upper panel right). However, Trp9 is useful as a reference marker for prostata carcinoma, i.e. can be used for quantifying the expression level of Trp8. The ratio of the expression of Trp8:Trp9 in patients and healthy individuals is useful for the development of a quantitative assay.

Example 10: Characterization of Trp10

The complete protein coding sequence of TRP10 (a and b) was determined by biocomputing (Fig. 10 and 11). Using a 235 bp fragment of the Trp10 cDNA as probe in Northern blot analysis TRP10 transcripts could only be detected in mRNA isolated from individuals with prostate cancer (Fig. 13, bottom panel) but not in mRNA isolated from benign tissue of the prostate (prostate BPH) nor in mRNA isolated from heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. The 235 bp cDNA fragment of the Trp10 cDNA was amplified using the primer pair UW248 5'-ACA GCT GCT GGT CTA TTC C-3' and UW249 5'-TAT

GTG CCT TGG TTT GTA CC-3' and prostate cDNA as template. In summary, Trp10a and Trp10b, like TRP8 are also expressed in malignant prostate tissue. So far, its expression could not be observed in any other tissue examined (see above). Thus, Trp 10a and Trp10b are also useful markers which are specific for malignant prostate tissue.

Furthermore, database searches in public databases of the national center for biological information (NCBI) revealed the existence of several expressed sequence tags (EST clones) being in part identical to the Trp10 sequence. These EST clones were originally isolated from cancer tissues of lung, placenta, prostate and from melanoma. These clones include the clones with the following accession numbers: BE274448, BE408880, BE207083, BE791173, AI671853, BE390627. The results demonstrate that cancer cells of these tissues express Trp10 related transcripts whereas no expression of Trp10 transcripts in the corresponding healthy tissues are detectable (Figure 13). Furthermore, it could be shown that in cancer cells of melanoma and prostate cancer Trp10 transcripts are expressed as shown by in situ hybridizations using 4 antisense probes (Figure 14A - E and 13K-O and Table 2, above). Furthermore, it could clearly be shown that cancer cells of these tissues expressing Trp10 transcripts also express Trp10-antisense transcripts as shown in Figure 14F-J, Figure 14P-R and Figure 14T by in situ hybridizations using 4 sense probes (Table 2, above). The in situ hybridization experiments demonstrate that detection of a subset of cancer cells derived from carcinoma of lung, placenta, prostate and melanoma is feasible using antisense as well as sense probes complementary to Trp10 transcripts or complementary to Trp10-antisense transcripts, respectively.

The foregoing is meant to illustrate but not to limit the scope of the invention. The person skilled in the art can readily envision and produce further embodiment, based on the above teachings, without undue experimentation.

What Is claimed Is:

1. An isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b or a protein exhibiting biological properties of Trp8a, Trp8b, Trp9, Trp10a or Trp10b and being selected from the group consisting of

- (a) a nucleic acid molecule encoding a protein that comprises the amino acid sequence depicted in Figure 7, 8A, 9, 10 or 11;
- (b) a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A,9, 10 or 11;
- (c) a nucleic acid molecule included in DSMZ Deposit No. DSM 13579, DSM 13580, DSM 13584, DSM 13581 or DSM....;
- (d) a nucleic acid molecule which hybridizes to a nucleic acid molecule specified in (a) to (c);
- (e) a nucleic acid molecule the nucleic acid sequence of which deviates from the nucleic sequences specified in (a) to (d) due to the degeneration of the genetic code; and
- (f) a nucleic acid molecule, which represents a fragment, derivative or allelic variation of a nucleic acid sequence specified in (a) to (e).
- 2. A recombinant vector containing the nucleic acid molecule of claim 1
- 3. The recombinant vector of claim 2 wherein the nucleic acid molecule is operatively linked to regulatory elements allowing transcription and synthesis of a translatable RNA in prokaryotic and/or eukaryotic host cells.
- 4. A recombinant host cell which contains the recombinant vector of claim 3.
- 5. The recombinant host cell of claim 4, which is a mammalian cell, a bacterial cell, an insect cell or a yeast cell.
- 6. An isolated protein exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b which is encoded by a nucleic acid molecule of claim 1.
- 7. A recombinant host cell that expresses the isolated protein of claim 6.

8. A method of making an isolated protein exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b comprising:

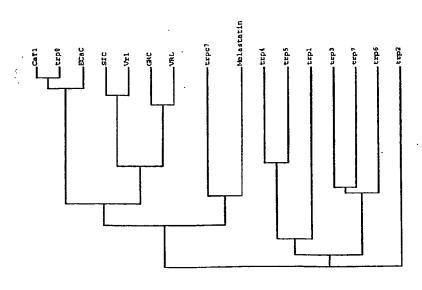
- (a) culturing the recombinant host cell of claim 6 under conditions such that said protein is expressed; and
- (b) recovering said protein.
- 9. The protein produced by the method of claim 8.
- 10. An antisense RNA sequence characterized in that it is complementary to an mRNA transcribed from a nucleic acid molecule of claim 1 or a part thereof and can selectively bind to said mRNA or part thereof, said sequence being capable of inhibiting the synthesis of the protein encoded by said nucleic acid molecule.
- 11. A ribozyme characterized in that it is complementary to an mRNA transcribed from a nucleic acid molecule of claim 1 or a part thereof and can selectively bind to and cleave said mRNA or part thereof, thus inhibiting the synthesis of the protein encoded by said nucleic acid molecule.
- 12. An inhibitor characterized in that it can suppress the activity of the protein of claim 6.
- 13. A method for diagnosing a prostate carcinoma which comprises contacting a target sample suspected to contain the protein Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA with a reagent which reacts with Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA and detecting Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA.
- 14. The method of claim 13, wherein the reagent is a nucleic acid.
- 15. The method of claim 13, wherein the reagent is an antibody.
- 16. The method of claim 13, wherein the reagent is detectably labeled.

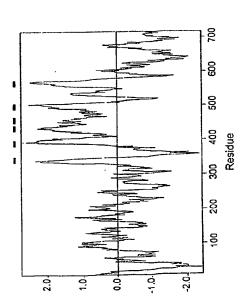
17. The method of claim 16, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

- 18. A method for diagnosing an endometrial cancer (carcinoma of the uterus) which comprises contacting a target sample suspected to contain the protein Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA with a reagent which reacts with Trp8a and/or Trp8b or the Trp8a and/or Trp8a and/or trp8b encoding mRNA and detecting Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA.
- 19. The method of claim 18, wherein the reagent is a nucleic acid.
- 20. The method of claim 18, wherein the reagent is an antibody.
- 21. The method of claim 18, wherein the reagent is detectably labeled.
- 22. The method of claim 21, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.
- 23. A method for diagnosing a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense RNA or Trp10a and/or Trp10b related antisense RNA.
- 24. A method for preventing, treating, or ameliorating a prostate tumor, endometrial cancer (carcinoma of the uterus) tumor, a chorion carcinoma, cancer of the lung or melanoma, which comprises administering to a mammalian subject a therapeutically effective amount of a reagent which decreases or inhibits expression of Trp8a, Trp8b, Trp10a and/or Trp10b and/or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b.
- 25. The method of claim 24, wherein the reagent is a nucleotide sequence comprising an antisense RNA.

26. The method of claim 24, wherein the reagent is a nucleotide sequence comprising a ribozyme.

- 27. The method of claim 24, wherein the reagent is an inhibitor of Trp8a, Trp8b, Trp10a and/or Trp10b.
- 28. The method of claim 27, wherein the reagent is an anti-Trp8a-, anti-Trp8b-, anti-Trp10a-and/or anti-Trp10b antibody or a fragment thereof.
- 29. A diagnostic kit useful for the detection of Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts in a sample, wherein the presence of an increased concentration of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts is indicative for a prostate tumor, endometrial cancer (cancer of the uterus) tumor, a chorion carcinoma, cancer of the lung or melanoma, said kit comprising a probe for detection of Trp8a, Trp8b, Trp9, Trp10a or Trp10b or Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts.
- 30. The kit of claim 29, wherein the target component to be detected is Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b and the probe is an antibody.
- 31. A method for identifying a compound which acts as an agonist or antagonist on the ion channels Trp8, Trp9 and/or Trp10, said method comprising contacting a test compound with the ion channel Trp8, Trp9 and/or Trp10, and determining whether said test compound affects the calcium uptake.



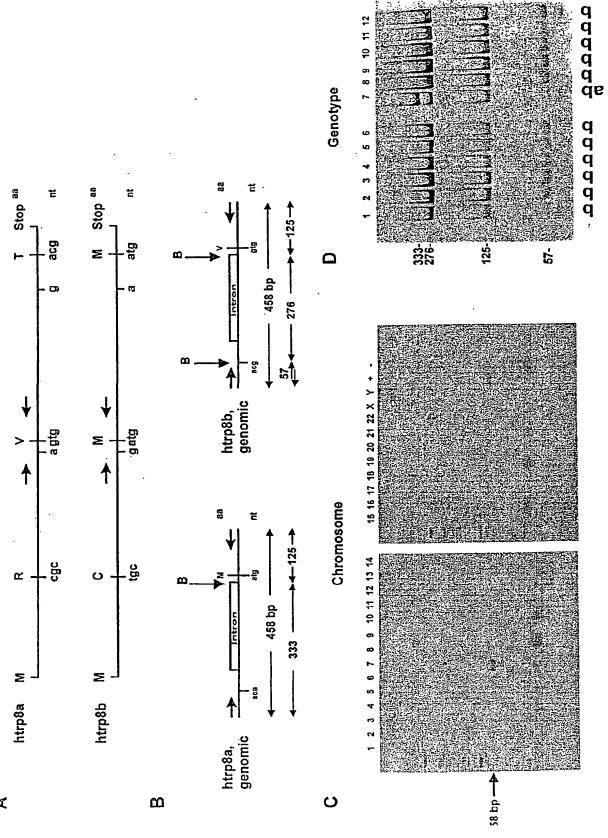


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Fig. 1

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Fig. 3

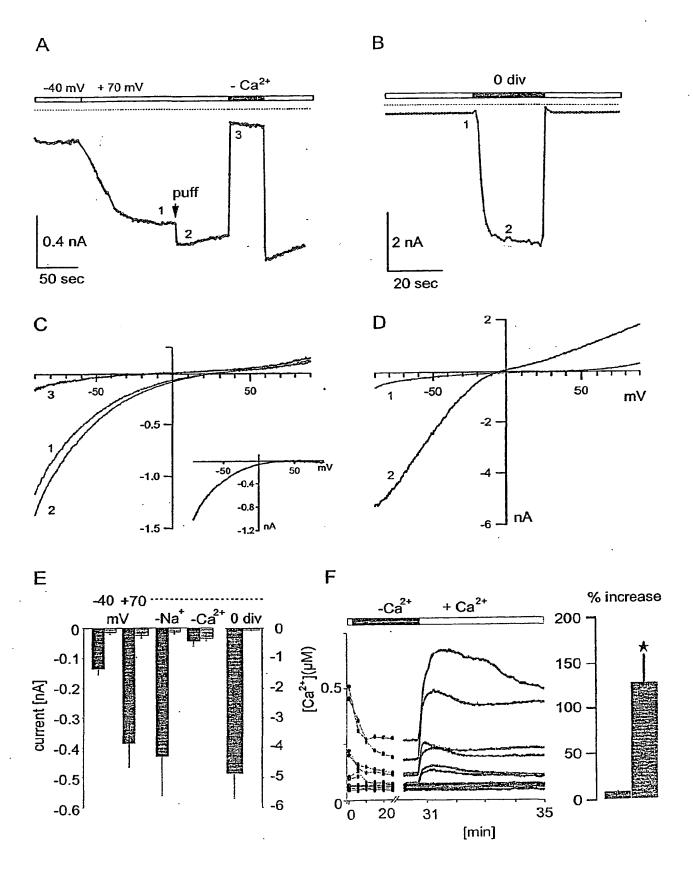
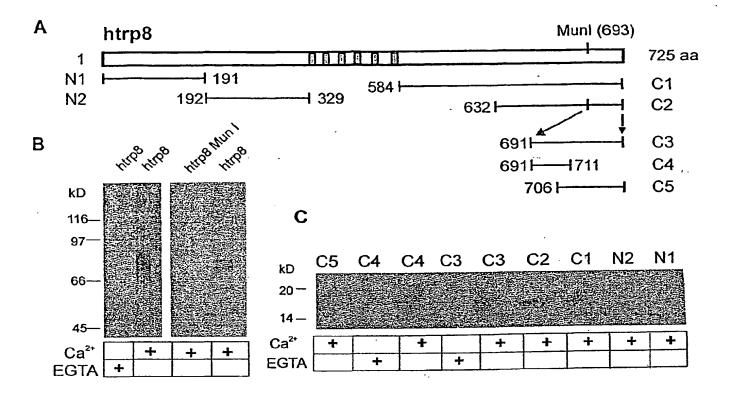


Fig. 4



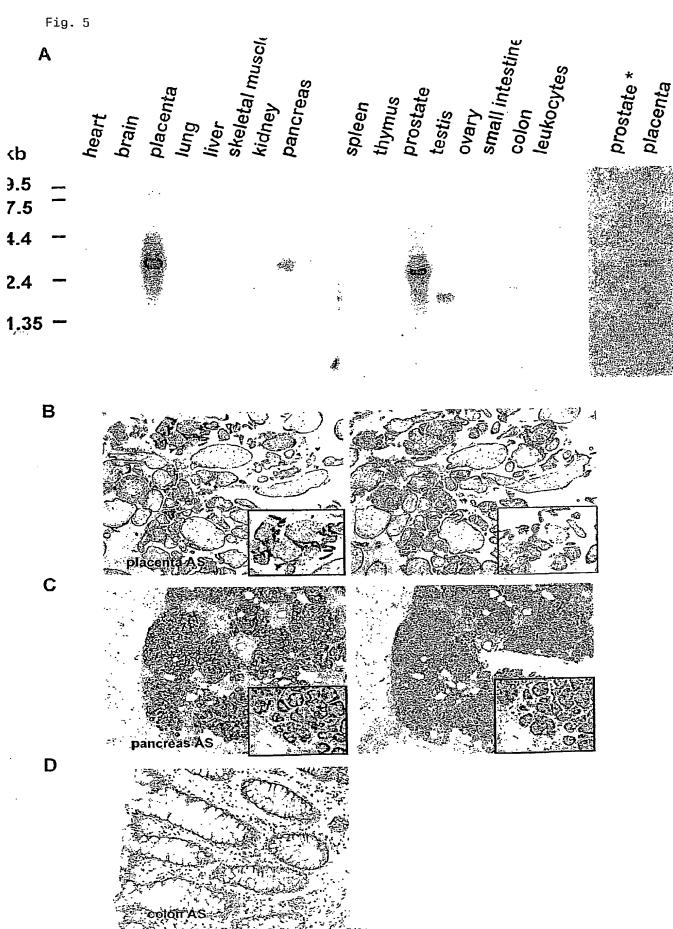


Fig. 6

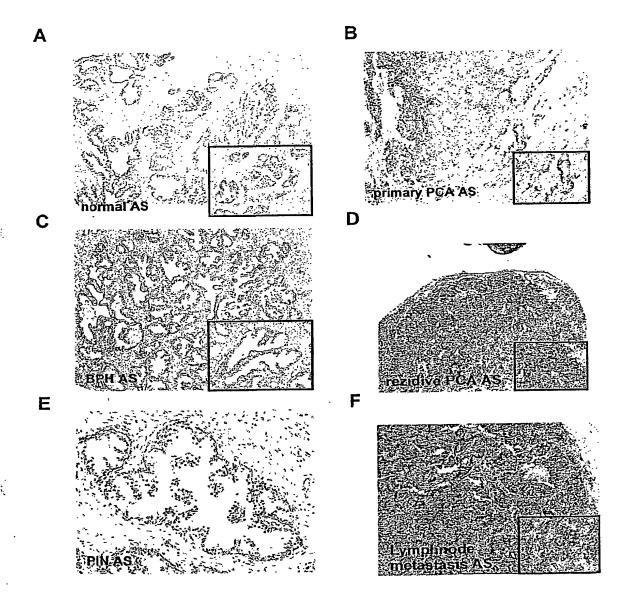


Fig. 7

GCCARGETGEARCANACTCACAGCCCTCTCCANACTGGCTGGGGCTGCTGGGAGACTCCCA 70 90 110 RGGACTCGTCAGGAAGCCAGGAGACAGGAGACAGGACCCTTTACAGGGAGACGGTGGGCCC 130 150 170 GGCCCTTGGGGGGGCTGATGTGGCCCCCAAGGAGCAGGACCCTCTACAGGGAGACGGTGGCCCCAAGGAGACAGCCCCATAGCCCCATAGGACCGCTCTGGCCTCGGCCC 130 210 230 CAGGCCCCCAAGGAGCCGGCCCTACACCCCCATGGGTTTGTCACTGGCCCCAAGGAGAAAGG 250 270 290 GCTAATTCTCTGCCTATGGAGCAAGTTCTTCACAGGGATTCTGGCCCTCGGCC L I L C L W S K F C R W F Q R R E S W A 310 330 355 CCAGAGCCCCAAGAACCAGCACCCTCTCGCCCAGGAGAGAGA		• •					20							50			
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190																	
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370	CCAGAG		TGAGC	AGAA	CCT	GCI		CAC	GAA	GAG	GAT	CTG	GGA	GTC'	TCC	CTC	CCT
CTAIGCTGCCAAAGATAATGATGTCCAGGCCCTGAACAAGTTGCTCAAGTATGAGGATTG L																	
L A A K B D N D V Q A L N K L L K Y E D C 430 430 450 470 470 470 470 A70 A70 A70 A7		370				-	390						4	10			
430	TCTAGO	TGCCAA	AGATA	ATGA	TGT	CCA	GGCC	CT	GAA	CAA	GTT	GCT	CAA				
CAAGGTGCACCAGAGAGGAGCCATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGA K V H Q R G A M G E T A L H I A A L Y D 490 510 530 CAACCTGGAGGCCGCCATGGTGCTGATGGAGGCTGCCCCGGAGCTGGTCTTTGAGCCCAT N L E A A M V L M E A A P E L V F E P M 550 570 590 GAACCTGGGGCCCTCTATGAGGGTCAGACTGCACTGCA	L A		D N	. D	V	Q		L	N	K	L	L		_	E	D .	С
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GACATCTCAGCTCTATGAGGGTCAGACTGCACTGCACATCGCTGTTGTAACCAGAACAT T S E L Y E G Q T A L H I A V V N Q N M 610 630 650 GAACCTGGTGCGACCCCTGCTTGCCCGCAGGGCCAGGCCACAGGCAC N L V R A L L A R R A S V S A R A T G T 670 690 710 TGCCTTCCGCCGTAGTCCCCGCAACCTCATCTACTTTGGGGAGCCACCAGGCAC A F R R S P R N L I Y F G E H P L S F A 730 7750 7770 TGCCTGTGTGAACAGTGAGGAGCACAGGCACCTCATCTACTTTGGGGAGCACCCCTTTGTCCTTTGC A F R R S P R N L I Y F G E H P L S F A 730 750 770 TGCCTGTGTGAACAGTGAGGAGACACTGAGGGCACCTCATTTACTTTGGGGAGCACCACGGCAC A C V N S E E I V R L L I E H G A D I R 790 810 830 GGCCCAGGACTCCCTGGGAACACAGTGTTACACATCCTCAACCACCACAAAAC A Q D S L G N T V L H I L I L Q P N K T 850 870 890 CTTTGCCTGCCAGATGTACAACCTGTTGCTGCTGCTGCCCAACACACAC																	
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TGCCTGTGTGACACGTGAGGAGATCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCG A C V N S E E I V R L L I E H G A D I R 790 810 830 GGCCCAGGACTCCCTGGGAAACACAGTGTTACACATCCTCATCCTCCAGCCCAACAAAC A Q D S L G N T V L H I L I L Q P N K T 850 870 890 CTTTGCCTGCCAGATGTACAACCTGTTGCTTGCTTCCTAGACACATGGGACCACCACAAAC F A C Q M Y N L L L S Y D R H G D H L Q 910 930 950 GCCCCTGGACCTCGTGCCCAATGTACAACCAGTGTTCCTACGACAGACA																	
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GCCCTGGACCTCGTGCCCATCCAGGGTCTCACCCCTTTCAGGTGGAGTGGA P L D L V P N H Q G L T P F K L A G V E 970 990 1010 GGGTAACACTGTGATGTTTCAGCACCTGATGCAGAGCGGAAGCACCCCAGTGGACGTA G N T V M F Q H L M Q K R K H T Q W T Y 1030 1050 1070 TGGACCACTGACCTCGACCTCTATGACCTCAGAGAGATCGACTCCTCAGGGGATGAGCA G P L T S T L Y D L T E I D S S G D E Q 1090 1110 1130 GTCCCTGCTGGAACTTATCATCACCACCAAGAGACCGGAGGCTCGCCAGATCCTGGACCA S L L E L I I T T K K R R E A R Q I L D Q 1150 1170 1190 GACGCCGGTGAAGGAGCTGGTGAGCCTCAAGTGCAGCGGTACCTCTCGGACCA T P V K E L V S L K W K R Y G R P Y F C 1210 1230 1250 CATGCTGGGTGCCATATATCTGCTGTACATCATCACCACCACTCCTCACCACTCCTCCCCAGTCCTCCCCACTCTCCCCACTCTCCCCACTCTCCCCCACTCTCCCCCC	F A	C Q	M	N	L	L	L	s	Y	D	R	H	G	D	H	L	Q
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GGGTAACACTGTGATGTTTCAGCACTGATGCAGAGCGGAAGCACCCAGTGGACGTA G N T V M F Q H L M Q K R K H T Q W T Y 1030	P L		V	P N	Н	Q			T	P	F	K			G	V	ь
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Fig. 7 / continuain 1

CCCCTCAAGCCCAGGACCAATAACCGCACAAGCCCCCGGGACAACACCCTCTTACAGCA 1350 1370 GAAGCTACTTCAGGAAGCCTACGTGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCT K L L Q E A Y V T P K D D I R L V G E L 1430 1410 1390 GGTGACTGTCATTGGGGCTATCATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAAT V T V I G A I I I L L V E V P D I F R M 1490 1470 GGGGGTCACTCGCTTCTTTGGACAGACCATCCTTGGGGGCCCATTCCATGTCCTCATCAT G V T R F F G Q T I L G G P F H V L I I 1530 1510 CACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCAGCGGGGA TYAFMVLVTMVNRLISASGE 1590 1610 1570 GGTGGTACCCATGTCCTTTGCACTCGTGCTGGGCTGCTACATCATCTACTTCGCCCG V V P M S F A L V L G W C N V M Y F A R 1650 AGGATTCCAGATGCTAGGCCCCTTCACCATCATGATTCAGAAGATGATTTTTGGCGACCT G F Q M L G P F T I M I Q K M I F G D L 1710 1690 GATGCGATTCTGCTGGCTGATGGCTGTGGTCATCCTGGGCTTTGCTTCAGCCTTCTATAT MRFCWLMAVVILGFASAFYI 1770 1790 1750 CATCTTCCAGACAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCT I F Q T E D P E E L G H F Y D Y P M A L 1850 1830 1810 GTTCAGCACCTTCGAGCTGTTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGA F S T F E L F L T I I D G P A N Y N V D 1870 1890 1910 CCTGCCCTTCATGTACAGCATCACCTATGCTGCCTTTGCCATCATCGCCACACTGCTCAT L P F M Y S I T Y A A F A I I A T L L M 1950 1930 GCTCAACCTCCTCATTGCCATGATGGGCGACACTCACTGGCGAGTGGCCCATGAGCGGGA L N L L I A M M G D T H W R V A H E R D 2010 2030 1990 TGAGCTGTGGAGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCG ELWRAQIVATTVMLERKLPR 2070 2050 CTGCCTGTGGCCTCGGCATCTGCGGACGGGAGTATGGCCTGGGGGACCGCTGGTT C L W P R S G I C G R E Y G L G D R W F 2150 2130 2110 CCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGC L R V E D R Q D L N R Q R I Q R Y A Q A 2190 2170 CTTCCACACCCGGGGCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGG F H T R G S E D L D K D S . V E K L E L G 2270 2250 CTGTCCCTTCAGCCCCCACCTGTCCCTTCCTACGCCCTCAGTGTCTCGAAGTACCTCCCG C P F S P H L S L P T P S V S R S T S R 2310 2330 2290 CAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGAGACCTGCGTGGGAT S S A N W E R L R Q G T L R R D L R G I 2390 2370 2350 AATCAACAGGGGTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCT INRGLEDGESWEYQI 2410 2430 2470 2490 AACACCCAGAGGTCTCATCTCCCAGGCCCCAGGGAGAAAGAGGAGTAGCATGAACGCCAA 2570 2550 GGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGCGGCAGA

Fig. 7 / continuation 2

GGAAGCCCAGCCCAAGCACGGGGCTGGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCA TCACCCTTCCGACAGGAGCACTGCATGTCAGAGCACTTTAAAAACAGGCCAGCCTGCTTG GGCCCTCGGTCTCCACCCCAGGGTCATAAGTGGGGAGAGAGCCCTTCCCAGGGCACCCAG TCTGGGGGTGGGAAGTGGGGCTAGGTCTTGCCAACTCCATCTTCAATAAAGTCGTTTTCG **GATCCCTAAAAAAAAAAAAAAAAAAAAAAAA**

MGLSLPKEKGLILCLWSKFCRWFQRRESWAQSRDEQNLLQQKRIWESPLLLAAKDNDVQALNKLLKYEDCKVHQRGAMGETALHIA
ALYDNLEAAMVLMEAAPELVFEPMTSELYEGQTALHIAVVNQNMNLVRALLARRASVSARATGTAFRRSPRNLIYFGEHPLSFAAC
VNSEEIVRLLIEHGADIRAQDSLGNTVLHILILQPNKTFACQMYNLLLSYDRHGDHLQPLDLVPNHQGLTPFKLAGVEGNTVMFQH
LMQKRKHTQWTYGPLTSTLYDLTEIDSSGDEQSLLELIITTKKREARQILDQTPVKELVSLKWKRYGRPYFCMLGAIYLLYIICFT
MCCIYRPLKPRTNNRTSPRDNTLLQQKLLQEAYVTPKDDIRLVGELVTVIGAIIILLVEVPDIFRMGVTRFFGQTILGGPFHVLII
TYAFMVLVTMVMRLISASGEVVPMSFALVLGWCNVMYFARGFOMLGPFTIMIQKMIFGDLMRFCWLMAVVILGFASAFYIIFQTED
PEELGHFYDYPMALFSTFELFLTIIDGPANYNVDLPFMYSITYAAFAIIATLLMLNLLIANMGDTHWRVAHERDELWRAQIVATTV
MLERKLPRCLWPRSGICGREYGLGDRWFLRVEDRQDLNRQRIQRYAQAFHTRGSEDLDKDSVEKLELGCPFSPHLSLPTPSVSRST
SRSSANWERLRQGTLRRDLRGIINRGLEDGESWEYOI

Figure 8:

ATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCT MGLSLPKEKGLILC 270 290 ${\tt GCCTATGGAGCAAGTTCTGCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAG}$ 330 350 ATGAGCAGAACCTGCTGCAGCAGAAGAGGATCTGGGAGTCTCCTCTCTTCTAGCTGCCA E Q N L L Q Q K R I W E S P L L L A A K 390 410 AAGATAATGATGTCCAGGCCCTGAACAAGTTGCTCAAGTATGAGGATTGCAAGGTGCACC D N D V Q A L N K L L K Y E D C K V H Q 430 450 470 AGAGAGGAGCCATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGG RGAMGETALHIAALYDNLEA 510 ${\tt CCGCCATGGTGCTGATGGAGCTGCCCCGGAGCTGGTCTTTGAGCCCATGACATCTGAGC}$ AMVLMEAAPELVFEPMTSEL 570 590 TCTATGAGGGTCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGC Y E G Q T A L H I A V V N Q N M N L V R 630 650 GAGCCCTGCTTGCCCGCAGGGCCAGTGTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCC A L L A R R A S V S A R A T G T A F R R 670 690 710 ${\tt GTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGCCTGTGTGA}$ S P C N L I Y F G E H P L S F A A C V N

Fig. 8 / contin 11

770 750 ACAGTGAGGAGATCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCGGGCCCAGGACT 810 830 790 L G N T V L H I L I L Q P N K T F A C Q 870 AGATGTACAACCTGTTGCTGTCCTACGACAGACATGGGGACCACCTGCAGCCCCTGGACC MYNLLLSYDRHGDHLQPLDL 910 930 950 V P N H Q G L T P F K L A G V E G N T V 990 1010 TGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACCCCAGTGGACGTATGGACCACTGA M F Q H L M Q K R K H T Q W T Y G P L T 1050 1070 CCTCGACTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGATGAGCAGTCCCTGCTGG STLYDLTEIDSSGDEQSLLE 1130 1110 AACTTATCATCACCACCAAGAAGCGGGAGGCTCGCCAGATCCTGGACCAGACGCCGGTGA LIITTKKREARQILDQTPVK 1170 1190 AGGAGCTGGTGAGCCTCAAGTGGAAGCGGTACGGCGCCGTACTTCTGCATGCTGGGTG ELVSLKWKRYGRPYFCMLGA 1230 1250 CCATATATCTGCTGTACATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGC I Y L L Y I I C F T M C C I Y R P L K P 1290 1310 CCAGGACCAATAACCGCACGAGCCCCCGGGACAACACCCTCTTACAGCAGAAGCTACTTC R T N N R T S P R D N T L L Q Q K L L Q 1370 1350 AGGAAGCCTACATGACCCCTAAGGACGATATCCGGCTGGTCGGGGGAGCTGGTGACTGTCA E A Y M T P K D D I R L V G E L V T V I 1410 1430 TTGGGGCTATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAATGGGGGTCACTC GAIIILLVEVPDIFRMGVTR 1470 GCTTCTTTGGACAGACCATCCTTGGGGGCCCATTCCATGTCCTCATCACCTATGCCT F F G Q T I L G G P F H V L I I T Y A F 1510 1530 1550 TCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCAGCGGGGAGGTGGTACCCA M V L V T M V M R L I S A S G E V V P M 1590 -1610 TGTCCTTTGCACTCGTGCTGGGCTGGTGCAACGTCATGTACTTCGCCCGAGGATTCCAGA S F A L V L G W C N V M Y F A R G F Q M 1650 TGCTAGGCCCCTTCACCATCATGATTCAGAAGATGATTTTTGGCGACCTGATGCGATTCT LGPFTIMIQKMIFGDLMRFC 1690 1710 1730 GCTGGCTGATGGCTGTGGTCATCCTGGGCTTTGCTTCAGCCTTCTATATCATCTTCCAGA WLMAVVILGFASAFYIIFQT 1770 1790 CAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCT EDPEELGHFYDYPMALFSTF 1830 1850 1810 TCGAGCTGTTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCA ELFLTIIDGPANYNVDLPFM 1890 1910 TGTACAGCATCACCTATGCTGCCTTTGCCATCATCGCCACACTGCTCATGCTCAACCTCC Y S I T Y A A F A I I A T L L M L N L L 1950 1970 TCATTGCCATGATGGGCGACACTCACTGGCGAGTGGCCCATGAGCGGGATGAGCTGTGGA

Fig. 8 / contion 2 IAMMGDTHWRVAHERDBLWR 2030 1990 2010 GGGCCCAGATTGTGGCCACCACGGTGATGCTGCAGCGGAAGCTGCCTCGCTGCCTGTGGC AQIVATTVMLERKLPRCLWP 2070 2090 CTCGCTCCGGGATCTGCGGACGGGAGTATGGCCTGGGAGACCGCTGGTTCCTGCGGGTGG R S G I C G R E Y G L G D R W F L R V E 2150 2110 2130 AAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCTTCCACACCC RQDLNRQRIQRYAQAFHTR 2170 2190 2210 GGGGCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCA SEDLDKDS V B K L E L G C P F S 2250 2270 GCCCCACCTGTCCCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCA H L S L P M P S V S R S T S R S S A N 2330 2310 2290 ATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGACCTGCGTGGGATAATCAACAGGG ERLROGTLRRDLRGIINRG 2390 2350 2370 GTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGA LEDGESWEYQI*

MGLSLPKEKGLILCLWSKFCRWFQRRESWAQSRDEQNLIQQKRIWESPLLLAAKDNDVQALNKLIKYEDCKVHQRGAMGETALHIA ALYDNLEAAMVLMEAAPELVFEPMTSELYEGQTALHIAVVNQNMNLVRALLARRASVSARATGTAFRRSPCNLIYFGEHPLSFAAC VNSEEIVRLLIEHGADIRAQDSLGNTVLHILILQPNKTFACQMYNLLSYDRHGDHLQPLDLVPNHQGLTPFKLAGVEGNTVMFQH LMQKRKHTQWTYGPLTSTLYDLTEIDSSGDEQSLLELIITTKKREARQILDQTPVKELVSLKWKRYGRPYFCMLGAIYLLYIICFT MCCIYRPLKPRTNNRTSPRDNTLLQQKLLQEAYMTPKDDIRLVGELVTVIGAIIILLVEVPDIFRMGVTRFFGQTILGGPFHVLII TYAFMVLVTMVMRLISASGEVVPMSFALVLGWCNVMYFARGFQMLGPFTIMIQKMIFGDLMRFCWLMAVVILGFASAFYIIFQTED PEELGHFYDYPMALFSTFELFLTIIDGPANYNVDLPFMYSITYAAFAIIATLLMLNLLIAMMGDTHWRVAHERDELWRAQIVATTV MLERKLPRCLWPRSGICGREYGLGDRWFLRVEDRQDLNRQRIQRYAQAFHTRGSEDLDKDSVEKLELGCPFSPHLSLPMPSVSRST SRSSANWERLRQGTLRRDLRGIINRGLEDGESWEYQI

B)

CAAACTCACAGCCCTCTCCAAACTGGCTGGGGGCTGCTGGGAGACTCCCAAGGAACTCGTCAGGAAGGCAGGAGACAGGAGACGGGA GGCCCCCAAGGAGCCGGCCCTACACCCCATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCTGCCTATGGAGCAAGTTCT GCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAGATGAGCAGAACCTGCTGCAGCAGAAGAGGATCTGGGAGTCTCCT CATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGGCCGCCATGGTGCTGATGGAGGCTGCCCCGGAGCTGG TCTTTGAGCCCATGACATCTGAGCTCTATGAGGGTCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGA GCCCTGCTTGCCCGCAGGGCCAGTGTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCCGTAGTCCCCGCAACCTCATCTACTTTGG GGAGCACCCTTTGTCCTTTGCCTGTGTGAACAGTGAGGAGATCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCGGGCCC TGCAGAAGCGGAAGCACACCCAGTGGACGTATGGACCACTGACCTCGACTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGAT GAGCAGTCCCTGCTGGAACTTATCATCACCACCAAGAAGCGGGAGGCTCGCCAGATCCTGGACCAGACGCCGGTGAAGGAGCTGGT GAGCCTCAAGTGGAAGCGGTACGGGCCGGTACTTCTGCATGCTGGGTGCCATATATCTGCTGTACATCATCTGCTTCACCATGT GCTGCATCTACCGCCCCCTCAAGCCCAGGACCAATAACCGCACAAGCCCCCGGGACAACACCCTCTTACAGCAGAAGCTACTTCAG GAAGCCTACGTGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCTGGTGACTGTCATTGGGGCTATCATCCTGCTGGTAGA GGTTCCAGACATCTTCAGAATGGGGGTCACTCGCTTCTTTGGACAGACCATCCTTGGGGGGCCCATTCCATGTCCTCATCATCACCT GCCCTGTTCAGCACCTTCGAGCTGGTCCTTACCATCATCGATGGCCCAACTACAACGTGGACCTGCCCTTCATGTACAGCAT CCCATGAGCGGGATGAGCTGTGGAGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGTGGCCT

Fig. 8 / continuation 3

c.)

CAAACTCACAGCCCTCTCCAAACTGGCTGGGGGCTGCTGGGAGACTCCCAAGGAACTCGTCAGGAAGGCAGGAGACAGGAGACGGGA CCTCTACAGGGAGACGGTGGGCCGGCCCTTGGGGGGGCTGATGTGGCCCCAAGGCTGAGTCCCGTCAGGGTCTGGCCTCGGCCTCA GGCCCCCAAGGAGCCGGCCCTACACCCCATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCTGCCTATGGAGCAAGTTCT GCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAGATGAGCAGAACCTGCTGCAGCAGAAGAGATCTGGGAGTCTCCT CTCCTTCTAGCTGCCAAAGATAATGATGTCCAGGCCCTGAACAAGTTGCTCAAGTATGAGGATTGCAAGGTGCACCAGAGAGGAGG CATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGGCCGCCATGGTGCTGATGGAGGCTGCCCCGGAGCTGG TCTTTGAGCCCATGACATCTGAGCTCTATGAGGTCCTGACTGCCCATCACTTGAACGCCTGCCCCTGAAATGCCAGGGCCTAGAG AAGAGGAAGAGATGGGCAGCAGCTGGATCCCCTGGGAATCCTGAACACCCGAGAGCTCCCTGTTCTCCATCCCAGGCTACCCCTGA TCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGAGCCCTGCTTGCCCGCAGGGCCAGTGTCTCTGCCA GAGCCACAGGCACTGCCTTCCGCCGTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGCTGTGAAC AGATGTACAACCTGTTGCTGTCCTACGACAGACATGGGGACCACCTGCAGCCCCTGGACCTCGTGCCCAATCACCAGGGTCTCACC CCTTTCAAGCTGGCTGGAGTGGAGGGTAACACTGTGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACACCCCAGTGGACGTATGG ACCACTGACCTCGACTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGATGAGCAGTCCCTGCTAGAACTTATCATCACCACCA $\tt TTCTGCATGCTGGGTGCCATATATCTGCTGTACATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAA$ TAACCGCACGAGCCCCCGGGACAACACCCTCTTACAGCAGAAGCTACTTCAGGAAGCCTACATGACCCCTAAGGACGATATCCGGC TGGTCGGGGAGCTGGTGACTGTCATTGGGGCTATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAATGGGGGTCACTCGC TTCTTTGGACAGACCATCCTTGGGGGCCCATTCCATGTCCTCATCATCACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCG GCTCATCAGTGCCAGCGGGGAGGTGGTACCCATGTCCTTTGCACTCGTGCTGGGCTGCTAACGTCATGTACTTCGCCCGAGGAT ATCCTGGGCTTTGCTTAGACAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCTTCGAGCT AGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGTGGCCTCGCTCCGGGATCTGCGGACGGGA GTATGGCCTGGGAGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCT TCCACACCCGGGGCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCAGCCCCCACCTGTCCCTT CCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGAGACCTGCG ${\tt TGGGATAATCAACAGGGGTCTGGAAGGACGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCTGGAACTT}$ GCTCTCATTTTCCTGGGTGCATCAAACAAAACAAAAACCAAACACCCAGGGTCTCATCTCCCAGGCCCCCAGGGAAAAGAGGAGT AGCATGAACGCCAAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGAAGCCCAGCC CAAGCACGGGGCTGGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCATCACCCTTCCGACAGGAGCACTGCATGTAGAGCACTT TAAAAACAGGCCAGCCTGCTTGGGCCCTCGGTCTCCACCCCAGGGTCATAAGTGGGGAGAGAGCCCTTCCCAGGGCACCCAGGCAG

D.)

Fig. 8 / continuation -

GATCGACTCCTCAGGGGATGAGCAGTCCCTGCTGGAACTTATCATCACCACCAAGAAGCGGGAGGCTCGCCAGATCCTGGACCAGA ATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAATAACCGCACAAGCCCCCGGGACAACACCCTCTTA CAGCAGAAGCTACTTCAGGAAGCCTACGTGACCCCTAAGGACGATATCCGGCTGGTCGGGGGGGCTGGTGACTGTCATTGGGGCTACATGTCCTCATCACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCAGCGGGGAGGTGGTACCCAT GTCCTTTGCACTCGTGCTGGGCTGCTACGTCATGTACTTCGCCCGAGGATTCCAGATGCTAGGCCCCTTCACCATCATGATTC TTCCAGACAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCTTCGAGCTGGTCCTTACCAT CATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCATCACCTATGCCGTTTGCCATCATCGCCACACTGC GGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCTTCCACACCCGGG GCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCAGCCCCCACCTGTCCCTTCCTACGCCCTCA GTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGACCTGCGTGGGATAATCAA ${\tt CAGGGGTCTGGAGGAGGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCTGGAACTTGCTCTCATTTTC}$ CTGGGTGCATCAAACAAAACAAAAACCAAACACCCAGAGGTCTCATCTCCCAGGCCCCCAGGGAGAAAGAGAGTAGCATGAACGCC AAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGCAAGCCCAAGCACGGGGC TGGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCATCACCCTTCCGACAGGAGCACTGCATGTCAGAGCACTTTAAAAACAGGCC GCAGAGCTTGTGGAAAGCGTGTGAGTGAGGGAGCAGGAACGGCTCTGGGGGTGGGAAGTGGGGCTAGGTCTTGCCAACTCCATCT

E.)

CACACATGGGGCCTCCCAGGAGTGCCCAGGACCTCGTGCTGTTGGCCTCTGAATCTATCGTCTCCAATCCGCTGTCCCACAGAAGC CATATAACCCACCTCTCTGTAAATGCCAGGAGCCATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGGCCG CCATGGTGCTGATGGAGGCTGCCCCGGAGCTGGTCTTTGAGCCCCATGACATCTGAGCTCTATGGAGGGTGAGGGCCCACGGGTCTG CCTACTCTTTTTSTCTTCTCTGTCTCCCTTCCGTGTCAGTCCCTGACTGCCCATCACTTGAACGCCTGCCCCCTGAAATGCCAGGG GCCTAGAGAAGAGAAGAGATGGGCAGCAGCTGGATCCCCTGGGAATCCTGAACACCCGAGAGCTCCCTGTTCTCCATCCCAGGCT $\tt CTGGGCCAGGTCAGACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGAGCCCTGCTTGCCCGCAGGGCCAGT$ GTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCCGTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGC CTGTGTGAACAGTGAGGAGATCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCGGGCCCAGGACTCCCTGGATGTACAACCTG TTGCTGTCCTACGACAGACATGGGGACCACCTGCAGCCCCTGGACCTCGTGCCCAATCACCAGGGTCTCACCCCTTTCAAGCTGGC TGGAGTGGAGGGTAACACTGTGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACACCCAGTGGACGTATGGACCACTGACCTCGA CTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGATGAGCAGTCCCTGCTGGAACTTATCATCACCACCAAGAAGCGGGAGGCT CGCCAGATCCTGGACCAGACGCCGGTGAAGGAGCTGGTGAGCCTCAAGTGGAAGCGGTACGGCCGGTACTTCTGCATGCTGGG TGCCATATATCTGCTGTACATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAATAACCGCACGAGCC CCCGGGACAACACCCTCTTACAGCAGAAGCTACTTCAGGAAGCCTACATGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCTG CATCCTTGGGGGCCCATTCCATGTCCTCATCACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCA GCGGGGAGGTGGTACCCATGTCCTTTGCACTCGTGCTGGGCTGGTGCAACGTCATGTACTTCGCCCGAGGATTCCAGATGCTAGGC TTCAGCCTTCTATATCATCTTCCAGACAGAGCCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCT TCGAGCTGGTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCATCACCTATGCTGCCTTT GCTGTGGAGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGGCCTCGCTCCGGGATCTGCG GACGGGAGTATGGCCTGGGAGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCA GTCCCTTCCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGG ACCTGCGTGGGATAATCAACAGGGGTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCT GGAACTTGCTCTCATTTTCCTGGGTGCATCAAACAAAAACAAAAACCAAACACCCAGAGGTCTCATCTCCCAGGCCCCAGGGAGAAA GAGGAGTAGCATGAACGCCAAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGAAG AGCACTTTAAAAACAGGCCAGCCTGCTTGGGCCCTCGGTCTCCACCCCAGGGTCATAAGTGGGGAGAGAGCCCCTTCCCAGGGCACC

Fig. 8 / continuation 5

Figure 9:

A.

30 CGGGGCCCTGGGCTGCAGGAGGTTGCGGCGGCCGCGGCAGCATGGTGCCGGAGAAGG M V V P E K E 110 90 AGCAGAGCTGGATCCCCAAGATCTTCAAGAAGAAGACCTGCACGACGTTCATAGTTGACT Q S W I P K I F K K K T C T T F I V D S 150 CCACAGATCCGGGAGGGACCTTGTGCCAGTGTGGGCGCCCCGGACCGCCCACCCCGCAG T D P G G T L C Q C G R P R T A H P A V .210 TGGCCATGGAGGATGCCTTCGGGGCAGCCGTGGTGACCGTGTGGGACAGCGATGCACACA 'AMEDAF.GAAVVTVWDSDAH.T 290 270 TEKPTDAYGELDFTGAGRKH 330 ACAGCAATTTCCTCCGGCTCTCTGACCGAACGGATCCAGCTGCAGTTTATAGTCTGGTCA S N F L R L S D R T D P A A V Y S L V . T 390 410 CACGCACATGGGGCTTCCGTGCCCCGAACCTGGTGGTGTCAGTGCTGGGGGGATCGGGGG R T W G F R A P N L V V S V L G G S G G 450 430 GCCCGTCCTCCAGACCTGCTGCAGGACCTGCTGCTGCGCTGGTGCGGGCTGCCCC PVLQTWLQDLLRRGLVRAAQ 510 530 STGAWIVTGGLHTGIGRHVG 550 570 590 GTGTGGCTGTACGGGACCATCAGATGGCCAGCACTGGGGGCACCAAGGTGGTGGCCATGG V A V R D H Q M A S T G G T K V V A M G 630 650 GTGTGGCCCCTGGGGTGTGGTCCGGAATAGAGACACCCTCATCAACCCCAAGGGCTCGT V A P W G V V R N R D T L I N P K G S F 710 690 TCCCTGCGAGGTACCGCTGGCGCGGTGACCCGGAGGACGGGGTCCAGTTTCCCCTGGACT PARYRWRGDPEDGVQFPLDY 770 730 750 ACAACTACTCGGCCTTCTTCCTGGTGGACGACGCCACACACGCTGCCTGGGGGGCGAGA N Y S A F F L V D D G T H G C L G G E N 810 830 R F R L R L E S Y I S Q Q K T G V G G T 890 870 CTGGAATTGACATCCCTGTCCTGCTCCTCGTTGATGATGGTGATGAGAAGATGTTGACGC G I D I P V L L L L I D G D E K M L T R 950 930 I E N A T Q A Q L P C L L V A G S G G A 990 1010 970 CTGCGGACTGCCTGGCGGAGACCCTGGAAGACACTCTGGCCCCAGGGAGTGGGGGAGCCA A D C L A E T L E D T L A P G S G G A R 1050 1070 GGCAAGGCGAAGCCCGAGATCGAATCAGGCGTTTCTTTCCCAAAGGGGACCTTGAGGTCC

Fig. 9 / continua - n 1

Q G E A R D R I R R F F P K G D L E V L 1130 1110 TGCAGGCCCAGGTGGAGAGGATTATGACCCGGAAGGAGCTCCTGACAGTCTATTCTTCTG $\begin{smallmatrix} Q & A & Q & V & E & R & I & M & T & R & K & E & L & L & T & V & Y & S & S & E \\ \end{smallmatrix}$ 1150 1170 1190 AGGATGGGTCTGAGGAATTCGAGACCATAGTTTTGAAGGCCCTTGTGAAGGCCTGTGGGA DGSEEFETIVLKALVKACGS 1230 1250 1210 GCTCGGAGGCCTCAGCCTACCTGGATGAGCTGCGTTTGGCTGTGGCTTGGAACCGCGTGG SEASAYLDELRLAVAWN RVD 1290 ${\tt ACATTGCCCAGAGTGAACTCTTTCGGGGGGGACATCCAATGGCGGTCCTTCCATCTCGAAG}$ I A Q S E L F R G D I Q W R S F H L E A 1330 1350 1370 $\tt CTTCCCTCATGGACGCCTGCTGAATGACCGGCCTGAGTTCGTGCGCTTGCTCATTTCCC$ 1410 1430 ACGGCCTCAGCCTGGGCCACTTCCTGACCCCGATGCGCCTGGCCCAACTCTACAGCGCGG 1450 1470 1490 $\tt CGCCCTCCAACTCGCTCATCCGCAACCTTTTGGACCAGGCGTCCCACAGCGCAGGCACCA$ PSNSLIRNLLDQASHSAGTK 1510 1530 ${\tt AAGCCCCAGCCCTAAAAGGGGGGGGCTGCGGAGCTCCGGCCCCCTGACGTGGGGCCATGTGC}$ A P A L K G G A A E L R P P D V G H V L 1590 1610 TGAGGATGCTGCTGGGGAAGATGTGCGCGCCGAGGTACCCCTCCGGGGGCGCCTGGGACC R M L L G K M C A P R Y P S G G A W D P 1650 1670 $\tt CTCACCCAGGCCAGGGCTTCGGGGGGGGGGCATGTATCTGCTCTCGGACAAGGCCACCTCGC$ HPGQGFGESMYLLSDKATSP. 1710 1730 $\tt CGCTCTCGCTGGATGCTGGCCTCGGGCAGGCCCCCTGGAGCGACCTGCTTCTTTGGGCAC$ L S L D A G L G Q A P W S D L L L W A L 1770 1790 ${\tt TGTTGCTGAACAGGGCACAGATGGCCATGTACTTCTGGGAGATGGGTTCCAATGCAGTTT}$ L L N R A Q M A M Y F W E M G S N A V S 1830 1850 1810 $\verb| CCTCAGCTCTTGGGGCCTGTTTGCTGCTCCGGGTGATGGCACGCCTGGAGCCTGACGCTG| \\$ S A L G A C L L L R V M A R L E P D A E 1890 1910 AGGAGGCAGCACGGAGGAAAGACCTGGCGTTCAAGTTTGAGGGGATGGGCGTTGACCTCT E A A R R K D L A F K F E G M G V D L F 1950 1970 $\tt TTGGCGAGTGCTATCGCAGCAGTGAGGTGAGGGCTGCCCGCCTCCTCCTCCGTCGCTGCC$ G E C Y R S S E V R A A R L L L R R C P 2010 2030 CGCTCTGGGGGGATGCCACTTGCCTCCAGCTGGCCATGCAAGCTGACGCCCGTGCCTTCT L W G D A T C L Q L A M Q A D A R A F F 2070 2090 2050 TTGCCCAGGATGGGGTACAGTCTCTGCTGACACAGAAGTGGTGGGGAGATATGGCCAGCA AQDGVQSLLTQKWWGDMAST 2150 2110 2130 CTACACCCATCTGGGCCCTGGTTCTCGCCTTCTTTTGCCCTCCACTCATCTACACCCGCC TPIWALVLAFFCPPLIYTRL 2210 2170 2190 ${\tt TCATCACCTTCAGGAAATCAGAAGAGGAGGCCCACACGGGAGGAGCTAGAGTTTGACATGG}$ I T F R K S E E E P T R E E L E F D M D 2270 2250 ATAGTGTCATTAATGGGGAAGGGCCTGTCGGGACGGGGACCCAGCCGAGAAGACGCCGC S V I N G E G P V G T A D P A E K T P L . 2310 2290

Fig. 9 / continue⇔ʻʻʻn 2

TGGGGGTCCCGCGCCAGTCGGGCCGTCCGGGTTGCTGCGGGGGCCGCTGCGGGGGCCCCC G V P R Q S G R P G C C G G R C G G R R 2370 2390 GGTGCCTACGCCGCTGGTTCCACTTCTGGGGCGTGCCGGTGACCATCTTCATGGGCAACG 2430 2450 TGGTCAGCTACCTGCTGCTTCCTGCTGCTTTTCTCGCGGGTGCTGCTCGTGGATTTCCAGC V S Y L L F L L F S R V L L V D F Q P 2490 2510 $\tt CGGCGCCGGCCCGGCTCCTGGAGCTGCTGCTCTATTTCTGGGCTTTCACGCTGCTGTGCG$ APPGSLELLLYFWAFTLLCE 2550 2570 AGGAACTGCGCCAGGGCCTGAGCGGAGGCGGGGGCAGCCTCGCCAGCGGGGGCCCCGGGC E L R Q G L S G G G G S L A S G G P G P 2610 2630 CTGGCCATGCCTCACTGAGCCAGCGCCTGCGCCTCTACCTCGCCGACAGCTGGAACCAGT G H A S L S Q R L R L Y L A D S W N Q C 2670 2690 GCGACCTAGTGGCTCTCACCTGCTTCCTCCTGGGCGTGGGCTGCCGGCTGACCCCGGGTT D L V A L T C F L L G V G C R L T P G L 2730 TGTACCACCTGGGCCGCACTGTCCTCTGCATCGACTTCATGGTTTTCACGGTGCGGCTGC Y H L G R T V L C I D F M V F T V R L L 2790 . 2810 TTCACATCTTCACGGTCAACAACAGCTGGGGCCCAAGATCGTCATCGTGAGCAAGATGA H I F T V N K Q L G P K I V I V S K M M 2850 2870 2830 TGAAGGACGTGTTCTTCTTCTTCTTCCTCGGCGTGTGGCTGGTAGCCTATGGCGTGG 2910 CCACGGAGGGCTCCTGAGGCCACGGGACAGTGACTTCCCAAGTATCCTGCGCCGCGTCT TEGLLRPRDSDFPSILRRVF 2970 2990 TCTACCGTCCCTACCTGCAGATCTTCGGGCAGATTCCCCAGGAGGACATGGACGTGGCCC Y R P Y L Q I F G Q I P Q E D M D V A L 3050 3030 TCATGGAGCACAGCAACTGCTCGGAGCCCGGCTTCTGGGCACACCCTCCTGGGGCCC MEHSNCSSEPGFWAHPPGAQ 3110 3090 AGGCGGCACCTGCGTCTCCCAGTATGCCAACTGGCTGGTGGTGCTGCTCCTCGTCATCT AGTCVSQYANNLVVLLLVIF 3170 3130 3150 TCCTGCTCGTGGCCAACATCCTGCTGGTCAACTTGCTCATTGCCATGTTCAGTTACACAT 3190 3210 ${\tt TCGGCAAAGTACAGGGCAACAGCGATCTCTACTGGAAGGCGCAGCGTTACCGCCTCATCC}$ G K V Q G N S D L Y W K A, Q R Y R L I R 3290 3270 GGGAATTCCACTCTCGGCCCGCCTGGCCCCGCCCTTTATCGTCATCTCCCACTTGCGCC E F H S R P A L A P P F I V I S H L R L 3330 3350 3310 TCCTGCTCAGGCAATTGTGCAGGCGACCCCGGAGCCCCCAGCCGTCCTCCCCGGCCCTCG L L R Q L C R R P R S P Q P S S P A L E 3410 3370 3390 AGCATTTCCGGGTTTACCTTTCTAAGGAAGCCGAGCGGAAGCTGCTAACGTGGGAATCGG 3450 3470 TGCATAAGGAGAACTTTCTGCTGGCACGCGCTAGGGACAAGCGGGAGAGCGACTCCGAGC H K E N F L L A R A R D K R E S D S E R 3510 3530 GTCTGAAGCGCACGTCCCAGAAGGTGGACTTGECACTGAAACAGCTGGGACACATCCGCG L K R T S Q K V D L A L K Q L G H I R E

Fig. 9 / continuer 1 3 3570 AGTACGAACAGCGCCTGAAAGTGCTGGAGCGGGAGGTCCAGCAGTGTAGCCGCGTCCTGG Y E Q R L K V L E R E V Q Q C S R V L G 3650 3610 3630 GGTGGCTGGCCGAGGCCCTGAGCCGCTCTGCCTTGCTGCCCCCAGGTGGGCCGCCACCCC WVAEALSRSALLPPGGPPP 3710 3670 3690 CTGACCTGCCTGGGTCCAAAGACTGAGCCCTGCTGGCGGACTTCAAGGAGAAGCCCCCAC DLPGSKD 3770 3730 3750 AGGGGATTTTGCTCCTAGAGTAAGGCTCATCTGGGCCTCGGCCCCCGCACCTGGTGGCCT 3810 3790 TGTCCTTGAGGTGAGCCCCATGTCCATCTGGGCCACTGTCAGGACCACCTTTGGGAGTGT 3850 3870 3890 CATCCTTACAAACCACAGCATGCCCGGCTCCTCCCAGAACCAGTCCCAGCCTGGGAGGAT 3910 3930 3950 CAAGGCCTGGATCCCGGGCCGTTATCCATCTGGAGGCTGCAGGGTCCTTGGGGTAACAGG 3990 4010 3970 GACCACAGACCCCTCACCACTCACAGATTCCTCACACTGGGGAAATAAAGCCATTTCAGA 4030 GGAAAAAAAAAAAAAAAAA

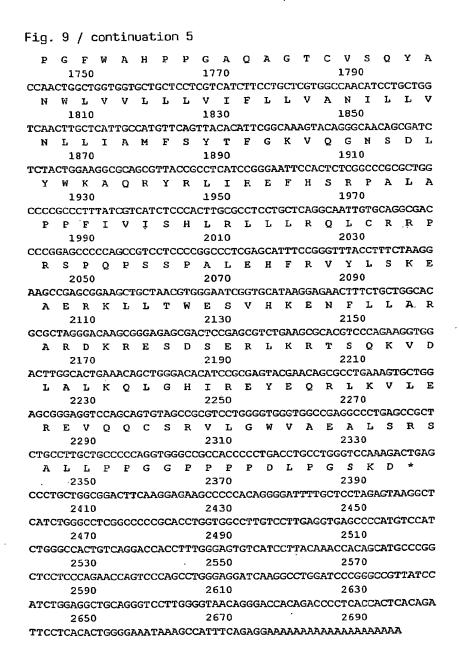
MVVPEKEQSWIPKIFKKKTCTTFIVDSTDPGGTLCQCGRPRTAHPAVAMEDAFGAAVVTVWDSDAHTTEKPTDAYELDFTGAG
SNFLRLSDRTDPAAVYSLVTRTWGFRAPNLVVSVLGGSGGPVLQTWLQDLLRRGLVRAAQSTGAWIVTGGLHTGIGRHVGVAV
QMASTGGTKVVAMGVAPWGVVRNRDTLINPKGSFPARYRWRGDPEDGVQFPLDYNYSAFFLVDDGTHGCLGGENRFRLRLESY
QKTGVGGTGIDIPVLLLLIDGDEKNLTRIENATQAHVPCLLVAGSRGLGMPGGTLEAHLAQDGDHKANQSTNQLLLPKDLSLQ
SIDRKTLQSYSERLAVAWNRVDIAQSELFRGDIQWRSFHLEASLMDALLNDRPEFVRLLISHGLSLGHFLTPMRLAQLYSAAF
LIRNLLDQASHSAGTKAPALKGGAAELRPPDVGHVLRMLLGKMCAPRYPSGGAWDPHPGQGFGESMYLLSDKATSPLSLDAGI
PWSDLLLWALLLINRAQMAMYFWEMGSNAVSSALGACLLLRVMARLEPDAEEAARRKDLAFKFEGMGVDLFGECYRSSEVRAAF
RRCPLWGDATCLQLAMQADARAFFAQDGVQSLLTQKWWGDMASTTPIWALVLAFFCPPLIYTRLITFRKSEEEPTREELEFDM
INGGGPVGTADPAEKTPLGVPRQSGRPGCCGGRGGRCLRRWFHFWGVPVTIFMGNVVSYLLFLLLFSRVLLVDFQPAPPGS
LLYFWAFTLLCEELRQGLSGGGGSLASGGPGFHASLSQRLRLYLADSWNQCDLVALTCFLLGVGCRLTPGLYHLGRTVLCII
FTVRLHIFTVNKQLGPKIVIVSKMMKDVFFFLFFLGVWLVAYGVATEGLLRPRDSDFPSILRRVFYRPYLQIFGQIPQEDMI
MEHSNCSSEPGFWAHPPGAQAGTCVSQYANWLVVLLLVIFILVANILLVNLLIAMFSYTFGKVQGNSDLYWKAQRYRLIREFF
ALAPPFIVISHLRLLLRQLCRRPRSPQPSSPALEHFRVYLSKEAERKLLTWESVHKENFILARARDKRESDSERLKRTSQKVI
KQLGHIREYEQRLKVLEREVQQCSRVLGWVAEALSRSALLPPGGPPPPDLPGSKD

в.)

10 30 50 ATCCAATGGCGGTCCTTCCATCTCGAAGCTTCCCTCATGGACGCCCTGCTGAATGACCGG 70 90 CCTGAGTTCGTGCGCTTGCTCATTTCCCACGGCCTCAGCCTGGGCCACTTCCTGACCCCG 170 130 150 ATGCGCCTGGCCCAACTCTACAGCGCGCGCCCCTCCAACTCGCTCATCCGCAACCTTTTG 190 210 230 GACCAGGCGTCCCACAGCGCAGGCACCAAAGCCCCAGCCCTAAAAGGGGGAGCTGCGGAG 270 290 250 CTCCGGCCCCTGACGTGGGGCATGTGCTGAGGATGCTGCTGGGGAAGATGTGCGCGCCG 330 350 AGATGTATCTGCTCTCGGACAAGGCCACCTCGCCGCTCTCGCTGGATGCTGGCCTCGGGC MYLLSDKATSPLSLDAGLGQ 370 390 410 ${\tt AGGCCCCTGGAGCGACCTGCTTCTTTGGGCACTGTTGCTGAACAGGGCACAGATGGCCA}$ APWSDLLLWALLLNRAQMAM 450 TGTACTTCTGGGAGATGGGTTCCAATGCAGTTTCCTCAGCTCTTGGGGGCCTGTTTGCTGC YFWEMGSNAVSSALGACLLL

Fig. 9 / continue 4

510 TCCGGGTGATGGCACGCCTGGAGCCTGACGCTGAGGAGGCAGCACGGAGGAAAGACCTGG RVMARLEPDAEEAARREDLA 590 570 CGTTCAAGTTTGAGGGGATGGGCGTTGACCTCTTTGGCGAGTGCTATCGCAGCAGTGAGG F K F E G M G V D L F G E C Y R S S E V 610 630 650 TGAGGGCTGCCCGCTCCTCCTCGCTGCCGCTCTGGGGGGATGCCACTTGCCTCC RAARLLLRRCPLWGDATCLQ 690 AGCTGGCCATGCAAGCTGACGCCCGTGCCTTCTTTGCCCAGGATGGGGTACAGTCTCTGC L A M Q A D A R A F F A Q D G V Q S L L 770 750 TGACACAGAAGTGGTGGGGAGATATGGCCAGCACTACACCCATCTGGGCCCTGGTTCTCG TQKWWGDMASTTPIWALVLA 810 790 CCTTCTTTTGCCCTCCACTCATCTACACCCGCCTCATCACCTTCAGGAAATCAGAAGAGG F F C P P L I Y T R L I T F R K S E E E 870 890 AGCCCACACGGGAGGAGCTAGAGTTTGACATGGATAGTGTCATTAATGGGGAAGGGCCTG PTREELEFDMDSVINGEGPV 930 950 TCGGGACGGGGCCCAGCCGAGAAGACGCCGCTGGGGGTCCCGCGCCAGTCGGGCCGTC G T A D P A E K T P L G V P R Q S G R P 990 1010 970 G C C G G R C G G R R C L R R W F H F W 1050 1070 GGGGCGTGCCGGTGACCATCTTCATGGGCAACGTGGTCAGCTACCTGCTGTTCCTGCTGC G V P V T I F M G N V V S Y L L F L L 1110 1130 1090 TTTTCTCGCGGGTGCTGCTCGTGGATTTCCAGCCGGCCCCCCCGGCTCCCTGGAGCTGC FSRVLLVDFQPAPPGSLELL 1170 1190 ${\tt TGCTCTATTTCTGGGCTTTCACGCTGCTGTGCGAGGAACTGCGCCAGGGCCTGAGCGGAG}$ L Y F W A F T L L C E E L R Q G L S G G 1250 1230 1210 GCGGGGCAGCCTCGCCAGCGGGGCCCCGGGCCTGGCCATGCCTCACTGAGCCAGCGCC G G S L A S G G P G P G H A S L S Q R L 1290 1310 1270 TGCGCCTCTACCTCGCCGACAGCTGGAACCAGTGCGACCTAGTGGCTCTCACCTGCTTCC RLYLADSWNQCDLVALTCFL 1330 1350 1370 TCCTGGGCGTGGGCTGCCGGCTGACCCCGGGTTTGTACCACCTGGGCCGCACTGTCCTCT LGVGCRLTPGLYHLGRTVLC 1410 I D F M V F T V R L L H I F T V N K Q L 1470 1490 TGGGGCCCAAGATCGTCATCGTGAGCAAGATGATGAAGGACGTGTTCTTCTTCCTCTCT G P K I V I V S K M M K D V F F F L F F 1530 1550 TCCTCGGCGTGTGGCTGGCCTATGGCGTGGCCACGGAGGGGCTCCTGAGGCCACGGG L G V W L V A Y G V A T E G L L R P R D 1590 1610 ACAGTGACTTCCCAAGTATCCTGCGCCGCGTCTTCTACCGTCCCTACCTGCAGATCTTCG S D F P S I L R R V F Y R P Y L Q I F G 1650 GGCAGATTCCCCAGGAGGACATGGACGTGGCCCTCATGGAGCACAGCAACTGCTCGTCGG Q I P Q E D M D V A L M E H S N C S S E 1710 AGCCCGGCTTCTGGGCACACCCTCCTGGGGCCCCAGGCGGCACCTGCGTCTCCCAGTATG



MYLLSDKATSPLSLDAGLGQAPWSDLLLWALLINRAQMAMYFWEMGSNAVSSALGACLLLRVMARLEPDAEEAARRKDLAFKFEGM
GVDLFGECYRSSEVRAARLLLRRCPLWGDATCLQLAMQADARAFFAQDGVQSLLTQKWWGDMASTTPIWALVLAFFCPPLIYTRLI
TFRKSEEEPTREELEFDMDSVINGEGPVGTADPAEKTPLGVPRQSGRPGCCGGRCGGRRCLRRWFHFWGVPVTIFMGNVVSYLLFL
LLFSRVLLVDFQPAPPGSLELLLYFWAFTLLCEELRQGLSGGGGSLASGGPGPGHASLSQRLRLYLADSWNQCDLVALTCFLLGVG
CRLTPGLYHLGRTVLCIDFMVFTVRLLHIFTVNKQLGPKIVIVSKMMKDVFFFLFFLGVWLVAYGVATEGLLRPRDSDFPSILRRV
FYRPYLQIFGQIPQEDMDVALMEHSNCSSEPGFWAHPPGAQAGTCVSQYANWLVVLLLVIFLLVANILLVNLLIAMFSYTFGKVQG
NSDLYWKAQRYRLIREFHSRPALAPPFIVISHLRLLLRQLCRRPRSPQPSSPALEHFRVYLSKEAERKLLTWESVHKENFLLARAR
DKRESDSERLKRTSQKVDLALKQLGHIREYEQRLKVLEREVQQCSRVLGWVAEALSRSALLPPGGPPPPDLPGSKD

Fig. 10

30 ATTAAACTTTATAAAACAGTGGCTGGATGGTTGGAGGATGCAGGTGGACAGAAGACGTGG MVGGCRWTEDVE 90 110 AGCCTGCAGAAGTAAAGGAAAAGATGTCCTTTCGGGCAGCCAGGCTCAGCATGAGGAACA PAEVKEKMSFRAARLSMRNR 150 130 GAAGGAATGACACTCTGGACAGCACCCGGACCCTGTACTCCAGCGCGTCTCGGAGCACAG RNDTLDSTRTLYSSASRSTD 210 230 ACTTGTCTTACAGTGAAAGCGCCAGCTTCTACGCTGCCTTCAGGACACAGACGTGCCCAA L S Y S E S A S F Y A A F R T Q T C P I 250 270 290 TCATGGCTTCTTGGGACTTGGTGAATTTTATTCAAGCAAATTTTAAGAAACGAGAATGTG MASWDLVNFIQANFKKRECV . 330 310 TCTTCTTTACCAAAGATTCCAAGGCCACGGAGAATGTGTGCAAGTGTGGCTATGCCCAGA F F T K D S K A T E N V C K C G Y A Q S 390 410 GCCAGCACATGGAAGGCACCCAGATCAACCAAAGTGAGAAATGGAACTACAAGAAACACA Q H M E G T Q I N Q S E K W N Y K K H T 470 430 450 CCAAGGAATTTCCTACCGACGCCTTTGGGGATATTCAGTTTGAGACACTGGGGAAGAAAG KEFPTDAFGDIQFETLGKKG 490 510 GGAAGTATATACGTCTGTCCTGCGACACGGACGCGGAAATCCTTTACGAGCTGCTGACCC K Y I R L S C D T D A E I L Y E L L T Q 570 AGCACTGGCACCTGAAAACACCCAACCTGGTCATTTCTGTGACCGGGGGGCGCCAAGAACT HWHLKTPNLVISVTGGAKNF 630 TCGCCCTGAAGCCGCGCATGCGCAAGATCTTCAGCCGGCTCATCTACATCGCGCAGTCCA ALKPRMRKIFSRLIYIAQSK 670 690 710 AAGGTGCTTGGATTCTCACGGGAGGCACCCATTATGGCCTGATGAAGTACATCGGGGAGG G A W I L T G G T H Y G L M K Y I G E V 730 750 770 TGGTGAGAGATAACACCATCAGCAGGAGTTCAGAGGAGAATATTGTGGCCATTGGCATAG V R D N T I S R S S E E N I V A I G I A 790 810 830 CAGCTTGGGGCATGGTCTCCAACCGGGACACCCTCATCAGGAATTGCGATGCTGAGGGCT A W G M V S N R D T L I R N C D A E G Y 890 870 850 ATTTTTTAGCCCAGTACCTTATGGATGACTTCACAAGAGATCCACTGTATATCCTGGACA F L A Q Y L M D D F T R D P L Y I L D N 930 ACAACCACACACTTTGCTGCTCGTGGACAATGGCTGTCATGGACATCCCACTGTCGAAG N H T H L L L V D N G C H G H P T V E A 1010 990 CAAAGCTCCGGAATCAGCTAGAGAAGTATATCTCTGAGCGCACTATTCAAGATTCCAACT K L R N Q L E K Y I S E R T I Q D S N Y 1070 1050 ATGGTGGCAAGATCCCCATTGTGTGTTTTGCCCAAGGAGGTGGAAAAGAGACTTTGAAAG G G K I P I V C F A Q G G K E T L K A 1130 1090 1110 CCATCAATACCTCCATCAAAAATAAAATTCCTTGTGTGGTGGTGGAAGGCTCGGGCCAGA I N T S I K N K I P C V V V E G S G Q I 1170 TCGCTGATGTGATCGCTAGCCTGGTGGAGGTGGAGGATGCCCTGACATCTTCTGCCGTCA A D V I A S L V E V E D A L T S S A V K 1230

AGGAGAAGCTGGTGCGCTTTTTACCCCGCACGGTGTCCCGGCTGCCTGAGGAGGAGACTG EKLVRFLPRTVSRLPEETE 1310 1290 1270 AGAGTTGGATCAAATGGCTCAAAGAAATTCTCGAATGTTCTCACCTATTAACAGTTATTA S W I K W L K E I L E C S H L L T V I K 1350 AAATGGAAGAAGCTGGGGATGAAATTGTGAGCAATGCCATCTCCTACGCTCTATACAAAG MEEAGDEIVSNAISYALYKA 1430 1410 CCTTCAGCACCAGTGAGCAAGACAAGGATAACTGGAATGGGCAGCTGAAGCTTCTGCTGG F S T S E Q D K D N W N G Q L K L L E 1490 1470 AGTGGAACCAGCTGGACTTAGCCAATGATGAGATTTTCACCAATGACCGCCGATGGGAGA W N Q L D L A N D E I F T N D R R W E K 1550 1530 1510 AGAGCAAACCGAGGCTCAGAGACACAATAATCCAGGTCACATGGCTGGAAAATGGTAGAA SKPRLRDTIIQVTWLENGRI 1590 TCAAGGTTGAGAGCAAAGATGTGACTGACGGCAAAGCCTCTTCTCATATGCTGGTGGTTC K V E S K D V T D G K A S S H M L V V L 1650 1670 ${\tt TCAAGTCTGCTGACCTTCAAGAAGTCATGTTTACGGCTCTCATAAAGGACAGACCCAAGT}$ KSADLQEVMFTALIKDRPKF 1710 TTGTCCGCCTCTTTCTGGAGAATGGCTTGAACCTACGGAAGTTTCTCACCCATGATGTCC V R L F L E N G L N L R K F L T H D V L 1770 1790 TCACTGAACTCTTCTCCAACCACTTCAGCACGCTTGTGTACCGGAATCTGCAGATCGCCA TELFSNHFSTLVYRNLQIAK 1830 AGAATTCCTATAATGATGCCCTCCTCACGTTTGTCTGGAAACTGGTTGCGAACTTCCGAA NSYNDALLTFVWKLVANFRR 1910 1870 1890 GAGGCTTCCGGAAGGAAGACAGAAATGGCCGGGACGAGATGGACATAGAACTCCACGACG G F R K E D R N G R D E M D I E L H D V 1950 TGTCTCCTATTACTCGGCACCCCCTGCAAGCTCTCTTCATCTGGGCCATTCTTCAGAATA SPITRHPLQALFIWAILQNK 2010 2030 AGAAGGAACTCTCCAAAGTCATTTGGGAGCAGACCAGGGGCTGCACTCTGGCAGCCCTGG KELSKVIWEQTRGCTLAALG 2090 2070 GAGCCAGCAAGCTTCTGAAGACTCTGGCCAAAGTGAAGAACGACATCAATGCTGCTGGGG ASKLLKTLAKVKNDINAAGE 2130 2150 AGTCCGAGGAGCTGGCTAATGAGTACGAGACCCGGGCTGTTGGTGAGTCCACAGTGTGGA SEELANEYETRAVGESTVWN 2190 2210 ATGCTGTGGTGGGCGCGGATCTGCCATGTGGCACAGACATTGCCAGCGGCACTCATAGAC A V V G A D L P C G T D I A S G T H R P 2270 2250 CAGATGGTGGAGAGCTGTTCACTGAGTGTTACAGCAGCGATGAAGACTTGGCAGAACAGC D G G E L F T E C Y S S D E D L A E Q L 2310 TGCTGGTCTATTCCTGTGAAGCTTGGGGTGGAAGCAACTGTCTGGAGCTGGCGGTGGAGG LVYSCEAWGGSNCLELAVEA 2370 2390 CCACAGACCAGCATTCATCGCCCAGCCTGGGGTCCAGAATTTTCTTAAGCAATGGT T D Q H F I A Q P G V Q N F L S K Q W Y 2450 2430 ATGGAGAGATTTCCCGAGACACCAAGAACTGGAAGATTATCCTGTGTCTGTTTATTATAC GEISRDTKNWKIILCLFIIP Fig. 10 / continuation 2

	2470						2490						2510	1			
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AGA#	ATGAGCA	GCG	CTG	GAG	GTG	GAT		STTC	GGT	CAT	CTA	CGZ	AGCC	CTA	CCT	'GGC	CA
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N	E Q	R	W	R	W	I	F R 3150	s	V	I	Y	Е	P 317	Y 0	L	A	M
N	E Q 3130	R	W	R	W	I	F R 3150	s	V	I	Y	Е	P 317 TTGC	Y O CCA	L	A	M
n TGTI	E Q 3130 CGGCCA	r GGT(V	W GCC	R CAG	W TGA	I CGT	ATTCCC F R 3150 GGATGC	S STAC	V	I GTA	Y TGA	E CT:	P 317 TTGC	Y O CCA H	CTG	A CAC	M
n TGTT F	E Q 3130 PCGGCCA G Q 3190	r GGT(V	W GCC P	R CAG S	W TGA D	I CGT V	F R 3150 GGATGO D G 3210	S STAC T	V CAC T	I GTA Y	Y TGA D	E .CT' F	P 317 TTGC A 323	Y O CCA H O	L CTC	A GCAC T	M CCT F
n TGTT F	E Q 3130 CCGCCA G Q	r GGT(V	W GCC P	R CAG S	W TGA D	I CGT V	F R 3150 GGATGO D G 3210	S STAC T	V CAC T	I GTA Y	Y TGA D	E .CT' F	P 317 TTGC A 323 ACAA	Y CCA H O	L CTC	A GCAC T	M CCT F
TGTT F	E Q 3130 CCGGCCA G Q 3190 CTGGGAA	R GGT0 V TGA0 E	W GCC P GTC	R CAG S CAA	W TGA D	I CGT V ACT	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT	S TTAC T	V CAC T	I GTA Y 'GGA	Y TGA D TGA	E .CT' F	P 317 TTGC A 323 ACAA	Y CCA H O CCT	C C C	A GCAC T	M CCT F
TGTT F TCAC	E Q 3130 PCGGCCA G Q 3190 CTGGGAA G N 3250	R GGT(V TGA(E	W GCC P GTC S	R CAG S CAA K	TGA D GCC P	I CGT V CACT L	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270	S T T TGGF E	V T AGCT	I CGTA Y Y CGGA D	Y TGA D TGA E	E CT' F .GC	P 3176 A 3236 ACAA N 329	Y O CCA H O CCT	CTG C GCC P	A GCAC T CCCC	M CCT F GGT F
TGTT F TCAC	E Q 3130 CGGCCA G Q 3190 CTGGGAA	R GGT(V TGA(E	W GCC P GTC S	R CAG S CAA K	TGA D GCC P	I CGT V CACT L	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270	S T T TGGF E	V T AGCT	I CGTA Y Y CGGA D	Y TGA D TGA E	E CT' F .GC	P 317 TTGC A 323 ACAA N 329	Y O CCA H CCT L O CAA	CTG C GCC P	A GCAC T CCCC	M CCT F GGT F
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TCAC T TCCC P TGGT V	E Q 3130 CCGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 CCAACCT N L 3370 AGGTCTG	R GGTG E GGTG I GGTG GGAAG	W GCC P GTC S CAC T GGT V GTT	R CAG S CAA K CAT I CGC A	W TGA D GCC P CCC P CCA M GGA GGA GGA GGA GGA GGA GGA GGA GGA	I CGT V CACT L CGTT F	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTGT V C 3330 TGGCTT G Y 3390 CTTCC	S T T T T T G G T A C A T T T T T T T T T T T T T T T	V CCAC T AGCT L CCTA Y V CGGT V	I CGTA Y CGGA D CAT M CGGG G	Y TGA D TGA E GTT L CAC	E CTT F .GC: H ATC S :CG' V	P 3176 A 3236 ACAA6 N 329 CCAC6 T 335 TCCA Q 341 GCAG	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA E 0 CCG	CTGCCP CCATI	A SCAC T CCCC R	M CCT F SGT F TGC L ATG D
TCAC T TCCC P TGGT V	E Q 3130 CCGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 CCAACCT N L 3370 AGGTCTG	R GGTC V TGAC E GATC I GCTC L GGAAC K	W GCC P GTC S CAC T GGT V GTT	R CAG S CAA K CAT I CGC A	W TGA D GCC P CCC P CCA M GGA GGA GGA GGA GGA GGA GGA GGA GGA	I CGT V CACT L CGTT F	ATTCCC F R 3150 GGATGC D G 3210 GTGTGC C V 3270 GGTGTC V C 3330 TGGCTT G Y 3390 CTTCCC F L	S T T T T T G G T A C A T T T T T T T T T T T T T T T	V CCAC T AGCT L CCTA Y V CGGT V	I CGTA Y CGGA D CAT M CGGG G	Y TGA D TGA E GTT L CAC	E CTT F .GC: H ATC S :CG' V	P 3176 A 3236 ACAA N 329 CCAC T 335 TCCA Q 341 GCAG	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA E 0 CCG	CTGCCP CCATI	A SCAC T CCCC R	M CCT F SGT F TGC L ATG D
TGTT F TCAC T TCCC P TGGT V ACCA	E Q 3130 CCGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 CCAACCT N L 3370 AGGTCTG V W 3430	R GGT(V TGA(E GAT(I GGAT(L GGAA(K	W GCC P GTC S CAC T GGT V GTT F	R CAG S CAA K CAT I CGC A CCCA	W TGA D GCC P CCC P CCA M GAC R	I CGTT L CGTT F GGTA	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTGT V C 3330 TGGCTT G Y 3390 CTTCCC F L 3450	S STAC T FGGF E SCAN I ACAC T	V CCAC T AGCTA Y CGGT V TGCA	I CGTA Y CGGA D ACAT M CGGG G AGGA E	Y TGA D TGA E GTT L CAC T	E CTT F .GCC H PATC S CCGC V	P 3176 A 3236 ACAA N 329 CCAC T 335 ICCA Q 341 GCAG S 347	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA E 0 CCG	L CTG C C GCC P GCAT I GAA N GCCT L	A GCAC R	M CCT F GGT F GGC L ATG D
TCCC TCCC TCCC TCCC TCCC TCCC TCCC TCCC	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430	R GGT0 V TGA0 E GAT0 I GGAA0 K	W GCC P GTC S CAC T GGT V GTT F CAT	R CAG S CAA K CAT I CGC A CCA Q	W TGA D GCC P CCAT M GAC R	I CGT V CACT L CGTT F GGTA Y	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTGT V C 3330 TGGCTT G Y 3390 CTTCC F L 3450	S STAC T FGGAT I ACAC T V FCTA	V CCAC T AGCT L CCTA Y CGGT V TGCA	I CGTA Y CGGA D LCAT M CGGG G AGGA E	Y TGA D TGA E GTT L CAC T GTA Y	E CTT F GCA H PATO S CCG V CT C	P 317/ 317/ A 323/ ACAA N 329 CCAC T 335 TCCA Q 341 GCAG S 347	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA E 0 CCG R 0 GT0	CTG C GCC P GCAT I GGA N GCCT L GCCT	A GCAC R CCCCC R CCCCC R N CCCCC N N CCCA N N CCCA N N CCCA N CCC	M CCT F SGT F TGC L ATG D
TGTT F TCAC T TCCC P TGGT V ACCA	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC	R GGTO V TGAO E GATO I GGAA K CCTTO F	W GCC P GTC S CAC T GGT V GTT F CAT	R CAG S CAA K CAT I CGC A CCA Q	W TGA D GCC P CCAT M GAC R	I CGT V CACT L CGTT F GGTA Y	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCT G Y 3390 CTTCC F L 3450 TTACT Y F	S STAC T FGGAT I ACAC T V FCTA	V CCAC T AGCT L CCTA Y CGGT V TGCA	I CGTA Y CGGA D LCAT M CGGG G AGGA E	Y TGA D TGA E GTT L CAC T GTA Y	E CTT F GCA H PATO S CCG V CT C	P 317/ 317/ A 323/ ACAA N 329/ CCAC T 3355 TCCA Q 341 GCAG S 347 AGAA K	Y OCCA H OCCT L OCCA N OCCA N OCCA OCCC R OCCC R OCCC C OC	CTG C GCC P GCAT I GGA N GCCT L GCCT	A GCAC R CCCCC R CCCCC R N CCCCC N N CCCA N N CCA N N CCA N N CCA	M CCT F SGT F TGC L ATG D
TGTT F TCAC T TCCC P TGGT V ACCA ACCA P TCCC	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P	R GGTTO V TGAO E GGATO I GGCTO K K CCTTO	W GCC P GTC S CAC T GGT V GTT F CAT	R CAG S CAA K CAT I CGC A CCA Q CGT V	W TGA D GCC P CCC P GCAT M GAC R CTT	I ACGT V CACT L CCCT F F GGTA Y	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCTA G Y 3390 CTTCCC F L 3450 TTACT Y F 3510	S T T T T G G A C A T T T T T T T T T T T T T T T T T	V CCAC T AGCT L Y CGGT V TGCA ACAT M	I CGTA Y CGGA D CAT M CGGG G G AGGA E V	Y TGA D TGA E GTT L GCAC T GGTA Y GGGT	E CT' F GCA H ATC C C C C C C K	P 317/ TTTGCC A 323/ ACAAN N 329/ CCACC T 335/ TCCAC Q 3411/ GCAG S 347/ AGAAA K 353	Y OCCA H OCCT L OCCA N OCCA N OCCA OCCC R OCCC R OCCC C OCCC OCCC OCC	CTG C GCC P CATI GAA N GCCT F	A GCACO R CCCCC R L ACAI N N CCAI K	M CCT F GGT F TGC L ATG D ATA I
TCCC P TCCC P TCCC P TCCC P TCCC P TCCC P	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA	R GGTC V TGAC E GATC I GGAA K CCTTC F	W GCC P GTC S CAC T GGTT F CAT I GAA	R CAG S CAA K CAT I CGC A CCA Q CGT V	W TGA D GCC P CCAT M GAC R CTT F	I CGT V CCCI L CGTT F GGT Y CGG	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510	S T T FGGF E ACAC T T FGGT V TCTF Y	V CCAC T AGCT L CCTA Y CGGT V CGGA ACAT M CCTC	I CGTA Y CGGA D ACAT M CGGG G CGGA CGGA CGGA CGGA CGGA CGGA	Y TGA D TGA E GTT L GTA Y TGGT V	E CTT F GCA H S CCG V CTT C C C C GA K	P 3177 3177 A 323 ACAA N 329 CCAC T 335 TCCA Q 341 GCAG S 347 AGAA K 353 GGTT	Y OCCA H OCCA OCCA OCCA OCCA OCCA OCCA OC	L CTG C P CAT I GAF N GCTT F	A GCAC R	M CCT F GGT F TGC L ATG D ATA I AGT C
TGTT F TCAC T TCCC P TGGT V ACCA ACCA P TCCC	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA	R GGTC V TGAC E GATC I GCTC K K CTTT F GGGAA E	W GCC P GTC S CAC T GGTT F CAT I GAA	R CAG S CAA K CAT I CGC A CCA Q CGT V	W TGA D GCC P CCAT M GAC R CTT F	I CGT V CCCI L CGTT F GGT Y CGG	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510 GGTCTT S S	S T T FGGF E ACAC T T FGGT V TCTF Y	V CCAC T AGCT L CCTA Y CGGT V CGGA ACAT M CCTC	I CGTA Y CGGA D ACAT M CGGG G CGGA CGGA CGGA CGGA CGGA CGGA	Y TGA D TGA E GTT L GTA Y TGGT V	E CTT F GCA H S CCG V CTT C C C C GA K	P 3177 3177 A 323 ACAA N 329 CCAC T 335 TCCA Q 341 GCAG S 347 AGAA K 353 GGTT F	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA C C C C T T T I	L CTG C P CAT I GAF N GCTT F	A GCAC R	M CCT F GGT F TGC L ATG D ATA I AGT C
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TCCC P TCCC P TCCC P TCCC P TCCC C TCCC P CTCCC C C ACTT	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA C K 3550	R GGTGAG E GGAAG K CCTT F GGGAAG E AGGAAG	W GCC P GTC S GAC T GGTT F CAT I GAA K AGC	R CAG S CAA K CAT I CGC A CCA Q CGT V AAA N	W TGA D GCC P CCC P CCAT M GAC R CTT F CAT	I CGTT L CGTT F GGTA Y CCGC A E	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510 GGTCTT S S 3570 TTTCA	S T T T G G T T T G T V T T T T T T T T T	V CCAC T L CCTA Y V CCGGI M CCTA M CCTA AAAGG	I CGTA Y CGGA D CAT M CGGG G CGGA C CGGGA CGGA CGGA CGGA CG	Y TGA D TGA E GTT L GCAC T GGT Y GGT V GGT E GCCT	E CT' F GC H CT' C C C C C K W GT' W	P 3170 A 3231 ACAAN N 329 CCACC T 335 TCCA Q 341 GCAGA K 353 GGTT F 359 ATCC	Y 0 CCA H 0 CCT L 0 CAA O GGA C C C C C C C C C C C C C C C C C C	L CTG C P CAT I I GAA N GCCT T F CCCA H	A CAMACAMAN N CCAMACAMAN N CCAM	M CCT F SGT F TGC L ATG D ATA I AGT C
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TCCC P	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA C K 3550 TGGGATC	R GGTC V TGAC E GATC I GGAA K CTTC F GGAA E GAAA E	W GCC P GTC S CAC T GGT F CAT I GAA K AGC	R CAG S CAA K CAT I CGC A CCA V AAA N CAA A	W TGA D GCC P CCAT M GGC R CTT F CAT M CGAT	I CGTT L CGTT F GGTA Y CGGGA TTTAA	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTG V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510 GTCTT C S 3570 TTTCA F R 3630	S STAC T FGGF E SCAN T V TCTF Y CCTGT V	V CCAC T L AGCT Y CGGT V Q ACAT M CGGT AAAGG	I CGTA Y CGGA D CAT M CGGG G CGGA C C C C C C C C C C C C C C	Y TGA D TGA E GTT L CCAC T V GTA Y GTA E GCCT L	E CT' F GC C C C C C C C C C C C C C C C C C	P 317/ TTGCC A 323/ ACAA N 329/ CCAC T 335/ TCCA Q 341/ GCAG S 347/ AGAA K 353/ GGTT F 359/ ATCC P 365	Y 0 CCA H 0 CCT L 0 CAA N 0 GGA C C C T T T 0 AGT V 0	CTGCCP CCAT I CCCTT F CCCP H	A GCAACAAA N N CCAA K V V FTGG G	M CCT F SGT F FGC L ATG D ATA I C TGT Y
TCCC P	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA C K 3550 TGGGATC	R GGTG V TGAG E GGATG I GGCTG K CCTTG CGGAA E CAGAA E	W GCC P GTC S CAC T GGT V GTT F AGA K AGC A	R CAG S CAA K CAT I CGC A CCA Q CGT V AAA N CAGC A GGCT GGCT GGCT GGCT GGCT GGCT GG	W TGA D GCC P CCAT M GAC R CTT F GAT I	I CGTT L CGTT F CGGTA Y CGGGTA N CGGGTA N CGGGTA N	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTGT V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510 GTCTT C S 3570 TTTCA F R 3630 GGACAT	S STAC T FGGF E SCAN I V V CTGF V CCGGGG	V CCAC T AGCT L CCGGT V CGGGT M CCGGGT AGCGG G CCAC G CCAC CCCAC CCCCAC CCCAC CCCAC CCCAC CCCAC CCCAC CCCAC CCCCAC CCCCAC CCCCAC CCCCCC	I CGTA Y CGGA D CAT M CGGG G C C C C C C C C C C C C	Y TGA D TGA E GTT L GTA Y GGTA Y GGTA E GCCT L	E CTT F GC H CTGA K GT W TGCA	P 3177 3177 323 323 329 329 329 320 335 347 353 365 37 359 37 365 365 27 365 20 37 37 37 37 37 37 37 37 37 37 37 37 37	Y 0 CCA H 0 CCT L 0 CCA N 0 GGA CCC R 0 GGC C TAT I 0 AGT V 0 CCA C	CTGCCP CAT I GGAP N GCCTT F CCCP H I GCCTT I I GCCT I I I GCCT I I I I I I I I I I I I I I I I I I	A CCAM	M CCT F GGT F GGC L ATG D ATA I AGT C GGT Y GAA S GCT
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TCCC P TCCC P TCCC P TCCC P TCCC C TCCC P GTTCC C C ACTT L	E Q 3130 FCGGCCA G Q 3190 CTGGGAA G N 3250 CCGAGTG E W 3310 FCAACCT N L 3370 AGGTCTG V W 3430 CCTTCCC F P 3490 GCTGCAA C K 3550 TGGGATC G S 3610 GGACCCC	R GGTG V TGAG E GGATG I GGCTG K CCTTG C GGAA E CAGA C C CAGA C C C C	W GCC P GTC S CAC T GGT V GTT F AGC A CTG	R CAG S CAA K CAT I CGC A CCA V AAA N CAGC A SGCT L	W TGA D GCC P CCAT M GAC R CTT F CAT M CGAT V	I CGTT L CGTT F CGGTA Y CGGGTA N CGGGTA N CGGGTA N	ATTCCC F R 3150 GGATGC D G 3210 GTGTGT C V 3270 GGTGTGT V C 3330 TGGCTT G Y 3390 CTTCC F L 3450 TTACT Y F 3510 GTCTT C S 3570 TTTCA F R 3630 GGACAT T S 3690	S STAC T FGGF E SCAN T V T FT V V CCTG T CCCAC T	V CCAC T AGCT L CCGGT V CGGGT M CCGGG AAAGC G R	I CGTA Y CGGA D CAT M CGGG G C C C C C C C C C C C	Y TGA D TGA E GTT L GTA Y GGTA E GCCT L	E CTT F GC GA GT GC T GC T GC T GC T GC T GC T	P 317/ TTGCC A 323/ ACAA N 329/ CCAC T 335/ TCCA Q 341/ GCAG S 347/ AGAA K 353/ GGTT F 359/ ATCC P 365/ CCATG C 371	Y OCCA H OCCT L OCCA N OCCA OCCA OCCA OCCA OCCA OCCA OC	CTGCP CATI GAAT FCCATI FCCATI ACTGCATA	A CAMAN N CAMAN V V CCGG G G	M CCT F SGT F TGC L ATG D ATA I AGT C TGT Y SAA S GCT W

Fig. 10 / continuation 3

MVGGCRWTEDVEPAEVKEKMSFRAARLSMRNRRNDTLDSTRTLYSSASRSTDLSYSESASFYAAFRTQTCPIMASWDLVNFIQANF
KKRECVFFTKDSKATENVCKCGYAQSQHMEGTQINQSEKWNYKKHTKEFPTDAFGDIQFETLGKKGKYIRLSCDTDAEILYELLTQ
HWHLKTPNLVISVTGGAKNFALKPRMRKIFSRLIYIAQSKGAWILTGGTHYGLMKYIGEVVRDNTISRSSEENIVAIGIAAWGMVS
NRDTLIRNCDAEGYFLAQYLMDDF'RDPLYILDNNHTHLLLVDNGCHGHPTVEAKLRNQIBKYISERTIQDSNYGGKIPIVCFAQG
GGKETLKAINTSIKNKIPCVVVEGSGQIADVIASLVEVEDALTSSAVKEKLVRFLPRTVSRLPEEETESWIKWLKEILECSHLLTV
IKMEEAGDEIVSNAISYALYKAFSTSEQDKDNNNGQLKLLLEWNQLDLANDEIFTNDRRWBKSKPRLRDTIIQVTWLENGRIKVES
KDVTDGKASSHMLVVLKSADLQEVMFTALIKDRPKFVRLFLENGLNLRKFLTHDVLTELFSNHFSTLVYRNLQIAKNSYNDALLTF
VWKLVANFRRGFRKEDRNGRDEMDIELHDVSPITRHPLQALFIWAILQNKKELSKVIWEQTRGCTLAALGASKLLKTLAKVKNDIN
AAGESEELANEYETRAVGESTVWNAVVGADLPCGTDIASGTHRPDGGELFTECYSSDEDLAEQLLVYSCEAWGGSNCLELAVEATD
CHFIAQPGVQNFLSKQWYGEISRDTKNWKIILCLFIIPLVGCISFVSFRKKPVDKHKKLLWYYVAFFTSPFVVFSWNVVFYIAFLLL
FAYVLLMDFHSVPHPPELVLYSLVFVLFCDEVRQGRPAAPSAGPAKPTPTRNSIWPASSTRSPGSRSRHSFHTSLQAEGASSGLGQ
PRKGWTFKNLEMVDISKLLMSLSVPFCTQWYVNGVNYFTDLWNVMDTLGLFYFIAGIVFRQGILRQNEQRWWIFRSVIYEPYLAM
FGQVPSDVDGTTYDFAHCTFTGNESKPLCVELDEHNLPRFPEWITIPLVCIYMLSTNILLVNLLVAMFGYTVGTVQENNDQVWKFQ
RYFLVQEYCSRLNIPFFIVFAYFYMVVKKCFKCCCKEKNMESSVCCEWFIHVYLGSEAAINFREGCLHPVIGSWTPGWLVWTSTR
ILTCSAGWPAAGSLSVTTHSSWYPAKSSKSOAHPDRTGRECDSASGWEGOPARWVEESVALFGHRGPVWPPTTLGITELNAPVL

в.

2310 2330 TGCTGGTCTATTCCTGTGAAGCTTGGGGTGGAAGCAACTGTCTGGAGCTGGCGGTGGAGG LVYSCEAWGGSNCLELAVEA 2350 2370 2390 T D Q H F I A Q P G V Q N F L S K Q W Y 2430 2450 ATGGAGAGATTTCCCGAGACACCAAGAACTGGAAGATTATCCTGTGTCTGTTTATTATAC G E I S R D T K N W K I I L C L F I I P 2470 2490 2510 CCTTGGTGGGCTGTGGCTTTGTATCATTTAGGAAGAACCTGTCGACAAGCACAAGAAGC LVGCGFVSFRKKPVDK

Figure 11:

a.) Trpl0b cDNA and derived amino acid sequence

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ATO	SAA	ATCCTT	CCT	TCC	TGT	CCA	CAC	CATCG'	TGCT	TAT	CAG	GGA(GAA	TGT	STG	CAA	STGT
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Y	I	G E	V	v	R	D	N	T I	s	R	S	S	E	E	И	I	V
		490						510						530			
GC	CAT'	rggca1	'AGC	AGC	TTG	ggg	CAT	GGTCT	CCAA	.CCG	GGA	CAC	CCI	CAT	CAG	GAA	TTGC
A	I	G I	A	A	W	G	M	v s	N	R	D	T	L	I	Ŕ	N	С
		550						570						590			
GA'	TGC'	rgaggg	CTA	بابليل	ידידידי	AGC	CCA	ama aa	ייי עייייי	GGA	TGA	CTT	CAC	CAAG	AGA	TCC	ACTG
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D	A	E G 610 CCTGGA L D	Y	F	L	A	Q	Y L 630 TTTGC L L	M TGCT	D	D GGA	F	Т	R 650 CTG C	D	P	ь
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TAT Y	A TATO I CAC	E G 610 CCTGGA L D 670 FGTCGA	Y .CAA N .AGC	F CAA N 'AAA	L .CCA H .GCT	A CAC. T CCG	Q ACA H GAA	Y L 630 TTTGC L L 690 TCAGC	M TGCT L TAGA	D CGT V GAA	D GGA D GTA	F CAA N TAT	T TGC G CTC	R 650 CTG C 710 CTGA	D FCA H GCG	P TGG G CAC	L ACAT H TATT
D TAT Y	A TAT(I	E G 610 CCTGGA L D 670	Y .CAA N	F .CAA N	L .CCA H	A CAC T	Q ACA H	Y L 630 TTTGC L L 690 TCAGC Q L	M TGCT L TAGA	D CGT V	D GGA D	F CAA N	T TGC G	R 650 CTG 710 CTGA	H CA'	P TGG G	L ACAT H
D TA' Y CCC	A TATO I CACT	E G 610 CCTGGA L D 670 FGTCGA V E 730	Y .CAA N .AGC	F CAA N AAA K	L CCA H GCT	A CAC T CCG R	Q ACA H GAA N	Y L 630 TTTGC L L 690 TCAGC Q L 750	M TGCT L TAGA E	D CGT V GAA K	D GGA D GTA Y	F CAA N TAT I	TGG G CTG S	R 650 CTG: 710 CTGA: E 770	D TCA' H GCG R	P TGG. G CAC T	L ACAT H TATT I
D TA' Y CCC	A TATO I CACT	E G 610 CCTGGA L D 670 TGTCGA V E	Y .CAA N .AGC	F CAA N AAA K	L CCA H GCT	A CAC T CCG R	Q ACA H GAA N	Y L 630 TTTGC L L 690 TCAGC Q L 750	M TGCT L TAGA E	D CGT V GAA K	D GGA D GTA Y	F CAA N TAT I	TGG G CTG S	R 650 CTG' 710 CTGA E 770	D TCA' H GCG R AGG	P TGG G CAC T	L ACAT H TATT I AAAA
D TA' Y CCC	A TATO I CACT	E G 610 CCTGGA L D 670 FGTCGA V E 730	Y .CAA N .AGC	F CAA N AAA K	L CCA H GCT	A CAC T CCG R	Q ACA H GAA N	Y L 630 TTTGC L L 690 TCAGC Q L 750	M TGCT L TAGA E TTGT	D CGT V GAA K	D GGA D GTA Y	F CAA N TAT I	TGG G CTG S	R 650 CTG: 710 CTGA: E 770	D TCA' H GCG R	P TGG. G CAC T	L ACAT H TATT I
TATY CCC P CAL Q	A I I CAC' T AGA'	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790	Y .CAA N .AGC A .CTA	F CAA N CAAA K TGG G	L CCA H GCT L TGG	A CAC. T CCG R CAA K	Q ACA' H GAA' N GAT I	Y L 630 FTTGC L L 690 FCAGC Q L 750 CCCCA P I 810	M TGCT L TAGA E TTGT	CGT V GAA K GTG	GGA D GTA Y TTT F	F CAA N TAT I TGC A	TGG G CTG S CC#	R 650 CTG 710 CTGA E 770 AAGG 830	D TCA' H GCG R AGG G	P TGG. G CAC T TGG	L ACAT H TATT I AAAA K
TATY CCC P CAL Q	A I I CAC' T AGA'	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790	Y .CAA N .AGC A .CTA	F CAA N CAAA K TGG G	L CCA H GCT L TGG	A CAC. T CCG R CAA K	Q ACA' H GAA' N GAT I	Y L 630 FTTGC L L 690 FCAGC Q L 750 CCCCA P I 810	M TGCT L TAGA E TTGT	CGT V GAA K GTG	GGA D GTA Y TTT F	F CAA N TAT I TGC A	TGG G CTG S CC#	R 650 CTG 710 CTGA E 770 AAGG 830	D TCA' H GCG R AGG G	P TGG. G CAC T TGG	L ACAT H TATT I AAAA K
TATY CCC P CAL Q GAG	A TATC T AGA' D GAC'	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790	Y .CAA N .AGC A .CTA Y	F.CAA N.CAA K.CAA K.TGG G.CAT	L CCA H GCT L TGG G	A CAC. T CCG R CAA K	Q ACA' H GAA' N GAT I	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA	M TGCT L TAGA E TTGT V	CGT V GAA K GTG C	GGA D GTA Y TTT F	F CAA N TAT I TGC A	TGG G CTG S CC# Q	R 650 CTG 710 CTGA E 770 AAGG 830	D TCA' H GCG R AGG G	P TGG. G CAC T TGG	L ACAT H TATT I AAAA K
TATY CCC P CAL Q	A I I CAC' T AGA'	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790 FTTGAA L K	Y .CAA N .AGC A .CTA	F CAA N CAAA K TGG G	L CCA H GCT L TGG	A CAC. T CCG R CAA K	Q ACA' H GAA' N GAT I	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K	M TGCT L TAGA E TTGT V	CGT V GAA K GTG	GGA D GTA Y TTT F	F CAA N TAT I TGC A	TGG G CTG S CC# Q	R 650 CTGA T10 E 770 AAGG B 830 STGT	D TCA' H GCG R AGG G	P TGG G TGG G GGT	L ACAT H TATT I AAAA K
TA' Y CCC P CAA Q GAC E	A TATO T T AGA' D GAC' T	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCGAA S N 790 ITTGGAA L K 850	Y .CAA N .AGC A .CTA Y .AGC	EAAA K TGG G CAT	L CCA H GCT L TGG G CAA	A CAC. T CCG R CAA K TAC	Q ACA' H GAA' N GAT I CTC	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870	M TGCT L TAGA E TTGT V AAAA N	D CGT V GAA K CTG C TAA K	GGA GTA Y TTT F AAT I	F CAA N TAT I TGC A	T TGG G CTG S CCA Q TTGG	R 650 CTG 710 E 770 AAGG B 830 STGT V 890	D TCA' H GCG R AGG G GGT V	P TGG G TGG G GGT V	L ACAT H TATT I AAAA K GGAA E
TATE	A IATO I CACT T AGAT D GACT T CTCC	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790 FTTGAA L K 850 GGGCCA	Y AGC A CTA Y AGC A A AGC A A AGC A A AGC A A A A	CAA N CAAA K TGG G CAT I	L CCA H GCT L TGG G CAA N	A CAC. T CCG R CAA K TAC T	Q ACA' H GAA' N GAT I CTC S	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K B70 CGCTA	M TGCT L TAGA E TTGT V AAAA N GCCT	CGT V GAA K GTG C TAA K	GGA GTA Y TTT F AAT I	F CAA N TAT I TGC A TCC P	T TGG G CTG S CC# Q TTG	R 650 CTG' 710 E 770 AAGG 830 STGT V 890	D TCA' H GCG R AGG G GT V	P TGG CAC T TGG G V CCT	L ACAT H TATT I AAAA K GGAA E
TA' Y CCC P CAA Q GAC E	A TATO T T AGA' D GAC' T	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790 FTTGAA L K 850 GGGCCA G Q	Y .CAA N .AGC A .CTA Y .AGC	EAAA K TGG G CAT	L CCA H GCT L TGG G CAA	A CAC. T CCG R CAA K TAC	Q ACA' H GAA' N GAT I CTC	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S	M TGCT L TAGA E TTGT V AAAA N GCCT	D CGT V GAA K CTG C TAA K	GGA GTA Y TTT F AAT I	F CAA N TAT I TGC A	T TGG G CTG S CCA Q TTGG	R 650 CTG' 710 E 770 AAGG 830 STGTC V 890 AGGA'	D TCA' H GCG R AGG G GGT V	P TGG G TGG G GGT V	L ACAT H TATT I AAAA K GGAA E
D TAY Y CCC P CAA Q GAA E GGG	A FIATO FIATO T AGA D GAC T CTC S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCAA S N 790 ITTGAA L K 850 GGGCCA G Q	Y CAAA N AGC A CTA Y AGC A GAT I	CAAA N K TGG G CAT I	L CCA H GCT TGG G CCAA N	A CAC. T CCGG R CAA K TAC T TGT V	Q ACA' H GAA N GAT I CTC S GAT I	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S	M TGCT L TAGA E TTGT V AAAA N GCCT L	D CGT V GAA K GTG C TAA K V	D GGA D GTA Y TTT F AAT I GGA E	CAAA N TAT I TGC A TCC P GGT V	TTGG G CTG S CCA Q TTG C GGA E	R 650 CTGA 710 E 770 AAGGA V 890 AGGA D	D TCA H GCG R AGG G GT V TGC	P TGGG G CAC T TGGG G CGT V CCT L	L ACAT H TATT I AAAA K GGAA E GACA T
D TA' Y CCC P CAA Q GAA E GGG	A ITATO T AGAC T AGAC T CTCC S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITCCAA S N 790 ITTGAA L K 850 GGGCA G Q 910 IGCCGI	Y CAA N AGC A CTA Y AGC A GAT I	F CAAA N AAAA K TTGG G CATT I CCGC A	L CCA H GCT L TGG G CCAA N TGAA D	A CAC. T CCG R CAA K TAC T TGT V GCT	Q ACA' H GAAA N GATT I CTC S GAT I	Y L 630 FTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA E 70 CGCTA S 930 GCGCT	M TGCT L TAGA E TTGT V AAAA N GCCT L	D CGT V GAA K GTG C TAAA K V CGTT	D GGA D GTA Y TTT F AAT I GGA E	F CAA N TAT I TGC A TCC P GGT V	TTGG G CTG S CCF Q TTGG C GGF	R 650 CTGA 710 E 770 AAGG 830 STGTC V 890 AGGA D 950	D TCA H GCG R AGG G TGC A CCG	P TGGG G CAC T TGG G C CCT L	L ACAT H TATT I AAAA K GGAA E GACA T GCCT
D TA' Y CCC P CAA Q GAA E GGG	A ITATO T AGAC T AGAC T CTCC S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCAA S N 790 ITTGAA L K 850 GGGCCA G Q	Y CAA N AGC A CTA Y AGC A GAT I	F CAAA N AAAA K TTGG G CATT I CCGC A	L CCA H GCT L TGG G CCAA N TGAA D	A CAC. T CCG R CAA K TAC T TGT V GCT	Q ACA' H GAAA N GATT I CTC S GAT I	Y L 630 FTTGC L L 690 FCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S 930 GCGCT R F	M TGCT L TAGA E TTGT V AAAA N GCCT L	D CGT V GAA K GTG C TAAA K V CGTT	D GGA D GTA Y TTT F AAT I GGA E	F CAA N TAT I TGC A TCC P GGT V	T TGG G CTG S CCF Q TTG C GGF E GGT V	R 650 CTGA T10 E 770 AAGG B30 STGTC 890 AGGA D 950 FGTC	D TCA H GCG R AGG G TGC A CCG	P TGGG G CAC T TGG G C CCT L	L ACAT H TATT I AAAA K GGAA E GACA T GCCT
TA'Y CCCP CAA Q GAA E GGG G TCCS	A ITATO I AGA T AGA D T CTCC S TTCC S	E G 610 CCTGGA L D 670 FGTCGA V E 730 FTCCAA S N 790 FTTGAA L K 850 GGGCCA G Q 910 FGCGGT A V 970	Y CAA N AGC A CTA Y AGC A GAT I CCAA	F CCAA N K TGG G CCAT I CCGC A	L CCAA H GCT L TGG G CCAA N TGAA D	A CAC T CCG R CAA K TAC T GGT U	Q ACA H GAA N GAT I CTC S GAT I GGT V	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 A S 930 GCGCT R F	M TGCT L TAGA E TTGT V AAAAA N GCCT L	D CGTT V GAA K CGTG C TAA K V CGTT V	D GGAA Y TTTT F AATT I GGAA E CCCG	F CAAA N TAT I TGC A TCC P GGT V	T TGG G CTG S CCF Q TTG C GGG E GGG V	R 650 C TGA TGA E 770 G G G G G G G G G G G TGTC V V 890 PSTC S S 1010	D TCA H GCG R AGG G V TGC A CCG R	P TGG G CAC T TGG G C T C T G G G C T L	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P
TA'Y CCCP CAA Q GAA E GGG G TCCS	A ITATO I AGA T AGA D T CTCC S TTCC S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITCCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGT A V	Y CAA N AGC A CTA Y AGC A GAT I CCAA	F CCAA N K TGG G CCAT I CCGC A	L CCAA H GCT L TGG G CCAA N TGAA D	A CAC T CCG R CAA K TAC T GGT U	Q ACA H GAA N GAT I CTC S GAT I GGT V	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 A S 930 GCGCT R F	M TGCT L TAGA E TTGT V AAAAA N GCCT L	D CGTT V GAA K CGTG C TAA K V CGTT V	D GGA D GTA Y TTTT F AAT I GGA E CCCG R	F CAA N TAT I TGC A TCC P CAC T TCT TTCT	TGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	R 650 C 710 TGAA F 770 AAGGA G B30 V 890 PGTGTC S L010	D TCA H GCG R AGG G GGT V TGC A CCG R	P TGG G CAC T TGG G CCT L GCT L	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P
TA'Y CCCP CAA Q GAA E GGG G TCCS	A ITATO I AGA T AGA D T CTCC S TTCC S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITCCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCGGT A V 970	Y CAAA N AGC A CTAA Y AGC A CCTAA CCTTAA CCTAA CCTTAA	F CCAA N K TGG G CCAT I CCGC A	L CCA H GCT L TGG G CAA N TGA L GGAA K TTGA K	A CAC. T CCG R CAA K TAC T GGT L GAT	Q ACA H GAA N GAT I CTC S GAT I GGT V CAA	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 A S 930 GCGCT R F	M TGCT L TAGA E TTGT V AAAAA N GCCT L TTTT L	D CGTT V GAA K CGTG C TAA K V CGGT V ACC	D GGA D GTA Y TTTT F AAT I GGA E CCCG R	F CAA N TAT I TGC A TCC P CAC T TCT TTCT	TTGG G CTG S CCF Q TTG C GGF E GGG C CGF E	R 650 C 710 C TGA E 770 AAGGA G 830 S 840 P 950 C TGTC S L010 AATG C C	D TCA H GCG R AGG G GGT V TGC A TTC S	P TGG G CAC T TGG G CCT L GCT L	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P
TA' Y CCC P CAA Q GAA E GGG TCC S GAA E	A FATCON S S GGA(E)	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITCCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGT A V 970 GGAGAC E T	Y CAA N AGC A CTA Y AGC A CCAA CCAA CCAA CCAA CCAA CCAA	F CAAA K TGG G CAT I CGGC A GGAA E	L CCA H GCT L TGG G CAA N TGA D GAA K TTTG	A CAC. T CCG R CAAA K TAC T GCT U GCT L GAT	Q ACA H GAA N GAT I CTC S GAT I CGC K CAA	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K B70 CGCTA A S 930 GCGCTA R F 990 ATGGC W L 1050	M TGCT L TAGA E TTGT V AAAAA N GCCT L TTTT L	D CGT V GAA K GTG C TAA K GGT V ACC P AGA E	GGA D GTA Y TTT F AAT I GGA E CCCG R	F CAA N TAT I TGC A TCC P GGT V CAC T TCT L	TTGG G CTG S CCF Q TTG C GGF E GGG C CGF E	R 650 CTGY- 710 TTGA- E 770 AAGG- G 830 ETGT- V V 950 D 950 CGTC- S L010 AATG- C	D TCA H GCG R AGG G TGC A CCG R TTC	P TGG G CAC T TGG G CCT L GCT L TCA	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P CCTA L
TA' Y CCC P CAA Q GAA E GGG TCC S GAA E	A FATCON S S GGA(E)	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITCCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGT A V 970 GGAGAC E T	Y CAA N AGC A CTA Y AGC A CCAA CCAA CCAA CCAA CCAA CCAA	F CAAA K TGG G CAT I CGGC A GGAA E	L CCA H GCT L TGG G CAA N TGA D GAA K TTTG	A CAC. T CCG R CAAA K TAC T GCT U GCT L GAT	Q ACA H GAA N GAT I CTC S GAT I CGC K CAA	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K B70 CGCTA A S 930 GCGCTA R F 990 ATGGC W L 1050	M TGCT L TAGA E TTGT V AAAAA N GCCT L TTTT L	D CGT V GAA K GTG C TAA K GGT V ACC P AGA E	GGA D GTA Y TTT F AAT I GGA E CCCG R	F CAA N TAT I TGC A TCC P GGT V CAC T TCT L	TTGG G CTG S CCF Q TTG C GGF E GGG C CGF E	R 650 CTGY- 710 TTGA- E 770 AAGG- G 830 ETGT- V V 950 D 950 CGTC- S L010 AATG- C	D TCA H GCG R AGG G TGC A CCG R TTC	P TGG G CAC T TGG G CCT L GCT L TCA	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P CCTA L
TAY Y CCC P CAA Q GAA E GGG TCC S GAA E TTT	A FATCO	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGI A V 970 GGAGAC E T 1030 AGTTAT	Y CAA N AGC A CTAA Y AGC A CTAA CTAA	F CAA N K TGG G CAT I CGC A GGA E GGA S AAT	L CCA H GCT L TGG G CAA N TGA K TTGA K TTTG	A CAC. T CCG R CAAA K TAC T GGT V GGT L GAT I AGA	Q ACA H GAA N GAT I CTC S GAT I CTC K AGC	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S 930 GCGCTA R F 990 ATGGC W L 1050 TGGGG	M TGCT L TAGA E TTGT V AAAAA N GCCT L TTTT L TCAA	D CGT V GAA K GTG C TAA K GGT V ACC P AGA E	GGA GTA Y TTTT F AAT I GGA E CCCG R AAT I	F CAA N TAT I TGC A TCC P GGT V CAC T TCT CTCT L	T TGG G CTG S CCF Q TTG C GGF E GGT C CGF E CGF	R 650 CTGY- 710 TTGA- E 770 AAGG- G 830 ETGT- V V 950 D 950 CGTC- S L010 AATG- C	D TCA' H GCG R AGG G GGT V TGC A TTC S CAT	P TGG G CAC T TGG G CCT L GCT L TCA	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P CCTA L
TA' Y CCC P CAA Q GAA E GGG TCC S GAA E	A FATCO	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGI A V 970 GGAGAC E T 1030 AGTTAT V I	Y CAA N AGC A CTAA Y AGC A CTAA CTAA	F CAA N K TGG G CAT I CGC A GGA E GGA S AAT	L CCA H GCT L TGG G CAA N TGA K TTGA K TTTG	A CAC. T CCG R CAAA K TAC T GGT V GGT L GAT I AGA	Q ACA H GAA N GAT I CTC S GAT I CAA K AGC A	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S 930 GCGCT R F 990 ATGGC W L 1050 TGGGG G D	M TGCT L TAGA E TTGT V AAAAA N GCCT L TTTT L TCAA	D CGT V GAA K GTG C TAA K GGT V ACC P AGA E	GGA GTA Y TTTT F AAT I GGA E CCCG R AAT I	F CAA N TAT I TGC A TCC P GGT V CAC T TCT CTCT L	TTGG G CTG S CCF Q TTG C GGF E GGT CCF CCF N	R 650 CTGA 710 TTGA E 770 AAGG G 830 ETGT V V V S 1010 ATGC C 1070 ATGC A	D TCA' H GCG R AGG G GGT V TGC A TTC S CAT I	P TGG G CAC T TGG G CCT L TCA H CCTC	L ACAT H TATT I AAAA K GGAA E GACA T GCCT P CCTA L
TA' Y CCC P CAL Q GA E GG G TC S GA E TT L	A FATCA S S S S S S S S S S S S S S S S S S S	E G 610 CCTGGA L D 670 IGTCGA V E 730 ITTCAA S N 790 ITTGAA L K 850 GGGCCA G Q 910 IGCCGI A V 970 GGAGAC E T 1030 AGTTAT	CAAA AGC A CTAA Y AGC A CTAA CCAAA K TTAA K	CAAA N CAAAA K TTGG G CATT I CGC A GGAA E GAG S AAT	L CCA H GCT L TGG G CCAA D GAA K TTGA K TTGA K TTGG K TTTG K TTGG	CAC. T CCG R CAA K TAC T GT V GCT L GAT I AGA	Q ACA' H GAA N GAT I CTC S GAT I CAA K AGC	Y L 630 TTTGC L L 690 TCAGC Q L 750 CCCCA P I 810 CATCA I K 870 CGCTA A S 930 GCGCT R F 990 ATGGC U 1050 TGGGGG D 1110	M TGCT L TAGA E TTGT V AAAA N GCCT L TCAA K ATGA	CGT V GAA K GTG C TAA K V ACC P AGA E AAI	GGA DGTA YTTT FAAT IGGA ECCG RAAT I	CAAA N TAT I TGC A TCC P GGT V CACC T TCT L GGGS	TTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	R 6550 C 7100 TGA E 7700 AAAGG B300 B300 V 8900 AGGA' D 950 C S L0100 AATG C C L1070 AATG C	D TCA H GCG R AGG G GT V TGC A TTC S CAT	P TGG G CAC T TGG G CCT L TCA H CCTC S	L ACAT H TATT I AAAA K GGAA T GCCT P CCTA L CTAC

Fig. 11 (Continuation)

		2410 2430										2450							
AGAAACTTAGGACCCAAGATTATAATGCTGCAGAGGATGCTGATCGATGTGTTCTTCTTC															CTTC				
R	N	L	G	P	K	I	I	M	L	Q	R	M	L	I	D	V	F	F	F
		24	70						249	0					2	510			
CT	CTGTTCCTCTTTGCGGTGTGGATGGTGGCCTTTGGCGTGGCCAGGCAAGGGATCCTTAGG																		
L	F	L	F	A	v	W	M	ν	A	F	G	v	A	R	Q	G	I	L	R
		25	30						255	0					2	570			
CA	GAA'	TGA	GCA	GCG	CTG	GAG	GTG	GAI	TTA	CCG	TTC	GGT	CAT	CTA	CGA	GCC	CTA	CCT	GGCC
Q	N	E	0	R	W	R	W	1	F	\mathbf{R}	s	v	I	Y	E	P	Y	L	A
~		25	90						261	0					2	630			
ATGTTCGGCCAGGTGCCCAGTGACGTGGATGGTACCACGTATGACTTTGCCCACTGCACC															CACC				
M	F	G	0	ν	P	s	D	v	D	G	т	т	Y	D	F	A	H	С	T
		26	50						267	0					2	690			
TT	CAC	TGG	GAA'	TGA	GTC	CAA	GCC	ACI	'GTG	TGT	GGA	GCT	GGA	TGA	GCA	CAA	CCT	GCC	CCGG
F	T	G	N	E	s	к	P	L	C	V	E	L	D	E	н	N	L	P	R
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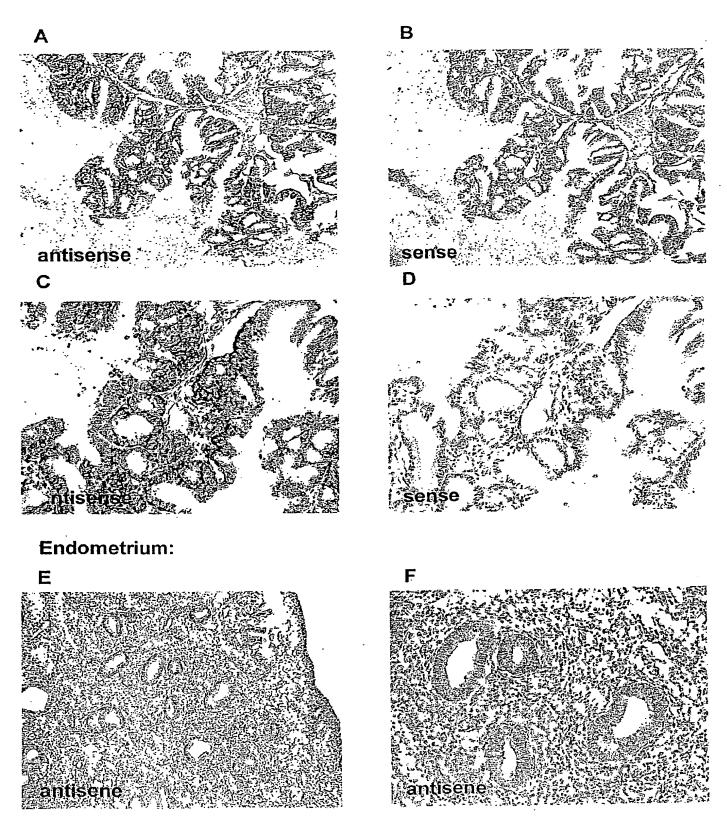
b.) Trp10 protein:

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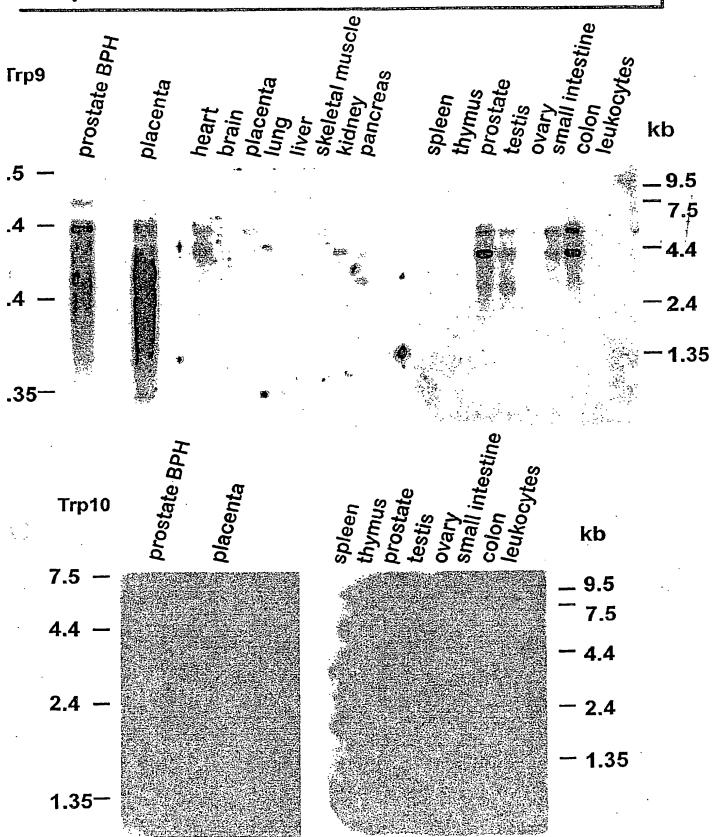
The Trp8 Gene is expre in normal endometrium

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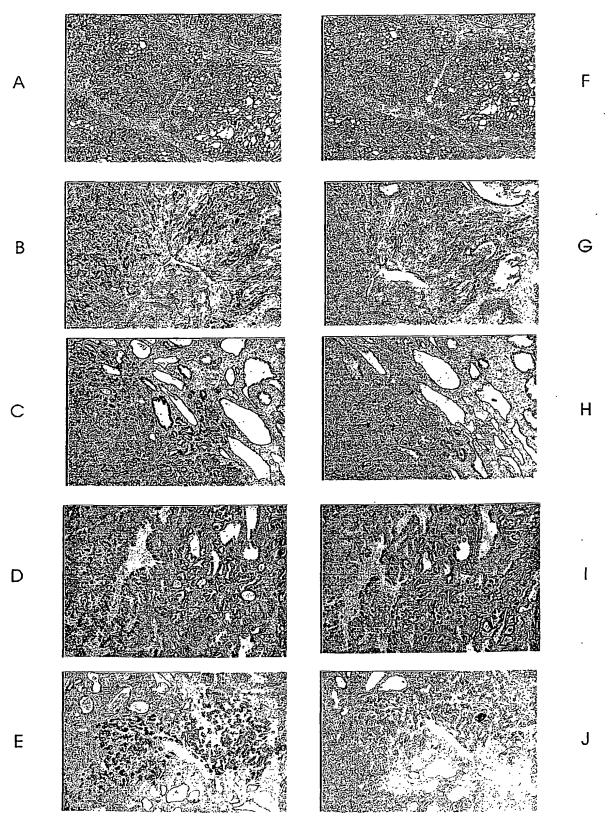
Endometrial cancer:



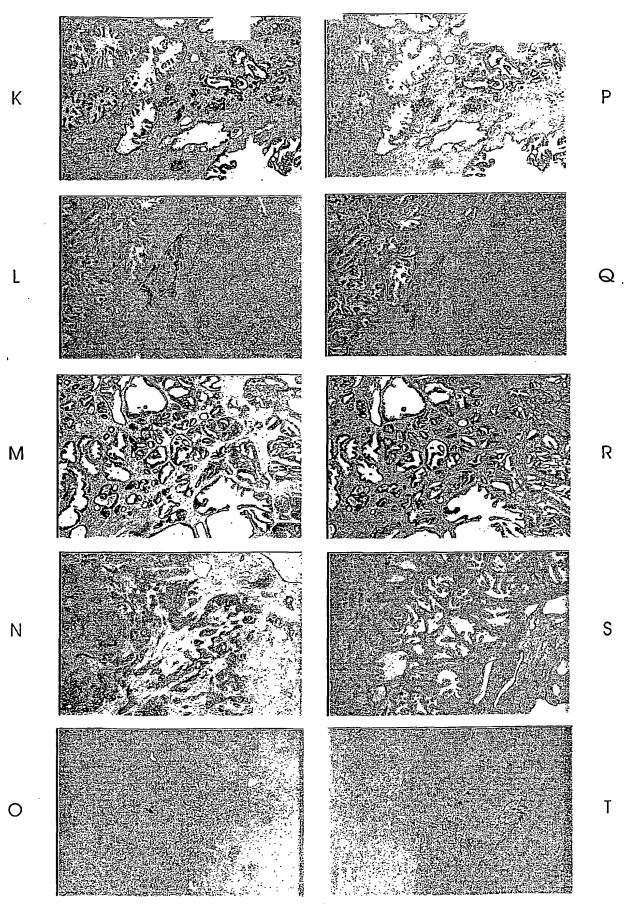
Expression of human Trp 9 and Irp 10



Expression of Trp10 transcripts and Trp10-antisense Transcripts in human prostate cancer and in malignant melanoma



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CORRECTED VERSION

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(54) Title: TRP8, TRP9 AND TRP10, NOVEL MARKERS FOR CANCER

(57) Abstract: The present invention relates to gene expression in normal cells and cells of malignant tumors and particularly to novel markers associated with cancer, Trp8, Trp9 and Trp10, and the genes encoding Trp8, Trp9 and Trp10. Also provided are vectors, host cells, antibodies, and recombinant methods for producing these human proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating a tumor.



Trp8, Trp9 and Trp10, novel markers for cancer

FIELD OF THE INVENTION

The present invention relates to gene expression in normal cells and cells of malignant tumors and particularly to novel markers associated with cancer, Trp8, Trp9 and Trp10, and the genes encoding Trp8, Trp9 and Trp10

BACKROUND OF THE TECHNOLOGY

Prostate cancer is one of the most common diseases of older men world wide. Diagnosis and monitoring of prostate cancer is difficult because of the heterogeneity of the disease. For diagnosis different grades of malignancy can be distinguished according to the Gleason-Score Diagnosis. For this diagnosis a prostate tissue sample is taken from the patient by biopsy and the morphology of the tissue is investigated. However, this approach only yields subjective results depending on the experience of the pathologist. For confirmation of these results and for obtaining an early diagnosis an additional diagnostic method can be applied which is based on the detection of a prostate specific antigen (PSA). PSA is assayed in serum samples, blood samples etc. using an anti-PSA-antibody. However, since in principle PSA is also expressed in normal prostate tissue there is a requirement for the definition of a threshold value (about 4 ng/ml PSA) in order to be able to distinguish between normal and malign prostate tissue. Unfortunately, this diagnostic method is quite insensitive and often yields false-positive results. Moreover, by using this diagnostic method any conclusions as regards the grade of malignancy, the progression of the tumor and its potential for metastasizing cannot be drawn. Thus, the use of molecular markers would be helpful to distinguish benign from malign tissue and for grading and staging prostate carcinoma, particularly for patients with metastasizing prostate cancer having a very bad prognosis.

The above discussed limitations and failings of the prior art to provide meaningful specific markers which correlate with the presence of prostate tumors, in particular metastasizing tumors, has created a need for markers which can be used diagnostically, prognostically and therapeutically over the course of this disease. The present invention fulfils such a need by the provision of Tpr8, Trp9 and Trp10 and the genes encoding Trp8, Trp9 and Trp10: The genes encoding Trp8 and Trp10 are expressed in prostate carcinoma and prostatic metastasis, but

not in normal prostate, benign hyperplasia (BHP) and intraepithelial prostatic neoplasia (PIN). Furthermore, expression of Trp10 transcripts is detectable in carcinoma but not in healthy tissue of the lung, the prostate, the placenta and in melanoma.

SUMMARY OF THE INVENTION

The present invention is based on the isolation of genes encoding novel markers associated with a cancer, Trp8, Trp9 and Trp10. The new calcium channel proteins Trp8, Trp9 and Trp10 are members of the trp (transient receptor potential) - family, isolated from human placenta (Trp8a and Trp8b) and humane prostate (Trp9, Trp10a and Trp10b). Trp proteins belong to a steadily growing family of Ca²⁺ selective and non selective ion channels. In the recent years seven Trp proteins (trp1 - trp7) have been identified and suggested to be involved in cation entry, receptor operated calcium entry and pheromone sensory signaling. Structurally related to the trp proteins are the vanilloid receptor (VR1) and the vanilloid like receptor (VRL-1) both involved in nociception triggered by heat. Furthermore, two calcium permeable channels were identified in rat small intestine (CaT1) and rabbit kidney (ECaC). These distantly related channels are suggested to be involved in the uptake of calcium ions from the lumen of the small intestine (CaT1) or in the reuptake of calcium ions in the distal tubule of the kidney (ECaC). Common features or the Trp and related channels are a proposed structure comprising six transmembrane domains including several conserved amino acid motifs. In the present invention the cloning and expression of a CaT1 like calcium channel (Trp8) from human placenta as well as Trp9 and Trp10 (two variants, Trp10a and Trp10b) is described. Two polymorphic variants of the Trp8 cDNA were isolated from placenta (Trp8a and Trp8b). Transient expression of the Trp8b cDNA in HEK (human embryonic kidney) cells results in cytosolic calcium overload implicating that the Trp8 channel is constitutive open in the expression system. Trp8 induces highly calcium selective inward currents in HEK cells. The C -terminus of the Trp8 protein binds calmodulin in a calcium dependent manner. The Trp9 channel is expressed in trophoblasts and syncytiotrophoblasts of placenta and in pancreatic acinar cells. Furthermore, the Trp8 channel is expressed in prostatic carcinoma and prostatic metastases, but not in normal tissue of the prostate. No expression of Trp8 transcripts is detectable in benign prostatic hyperplasia (BPH) or prostatic intraepithelial neoplasia (PIN). Therefore, the Trp8 channel is exclusively expressed in malign prostatic tissues and serves as molecular marker for prostate cancer. From the experimental results it is also apparent that the

modulation of Trp8 and/or Trp10, e.g. the inhibition of expression or activity, is of therapeutic interest, e.g. for the prevention of tumor progression.

The present invention, thus, provides a Trp8, Trp9 and Trp10 protein, respectively, as well as nucleic acid molecule encoding the protein and, moreover, an antisense RNA, a ribozyme and an inhibitor, which allow to inhibit the expression or the activity of Trp8, Trp9 and/or Trp10.

In one embodiment, the present invention provides a diagnostic method for detecting a prostate cancer or endometrial cancer (cancer of the uterus) associated with Trp8 or Trp10 in a tissue of a subject, comprising contacting a sample containing Trp8 and/or Trp10 encoding mRNA with a reagent which detects Trp8 and/or Trp10 or the corresponding mRNA.

In a further embodiment, the present invention provides a diagnostic method for detecting a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense transcripts or Trp10a and/or Trp10b related antisense transcripts.

In another embodiment, the present invention provides a method of treating a prostate tumor, carcinoma of the lung, carcinoma of the placenta (chorion carcinoma) or melanoma associated with Trp8 and/or Trp10, comprising administering to a subject with such an disorder a therapeutically effect amount of a reagent which modulates, e.g. inhibits, expression of Trp8 and/or Trp10 or the activity of the protein, e.g. the above described compounds.

Finally, the present invention provides a method of gene therapy comprising introducing into cells of a subject an expression vector comprising a nucleotide sequence encoding the above mentioned antisense RNA or ribozyme, in operable linkage with a promoter.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: A, phylogenetic relationship of trp and related proteins. B, hydropathy plot of the Trp8 protein sequence according to Kyte and Doolittle. C, alignment of Trp8a/b to the epithelial calcium channels ECaC (from rabbit) and Vr1 (from rat). Putative transmembrane domains are underlined.

Figure 2: A, polymorphism of the Trp8 gene. The polymorphic variants Trp8a and Trp8b differ in five base pairs resulting in three amino acid exchanges in the derived protein sequences. Specific primers were derived from the Trp8 gene as indicated by arrows. B, the Trp8a and Trp8b genes are distinguishable by a single restriction site. Genomic fragments of the Trp8 gene can be amplified using specific primers (shown in A). The genomic fragment of the Trp8b gene contains an additional site of the restriction enzyme BSP1286I (B). C, the Trp8 gene is located on chromosome 7. D, genotyping of eleven human subjects. A 458 bp genomic fragment of the Trp8 gene was amplified using specific primers (shown in A) and restricted with BSP1286I. The resulting fragments were analyzed by PAGE electrophoresis.

Figure 3: The Trp8b protein is a calcium selective ion channel. A, representative trace of a pdiTrp8b transfected HEK 293 cell. Trp8b mediated currents are activated by voltage ramps (-100 mV - +100 mV) of 100 msec at -40 mV or +70 mV holding potential. 1, Trp8b currents in the presence at 2mm $[Ca^{2+}]_0$; 2, effect of solution switch alone 3, switch to nominal zero calcium solution. B, Trp8b currents in the presence of zero divalent cations. C, current voltage relationship of the currents shown in A. Inset, leak subtracted current. D, current voltage relationship of the current shown in B. E, statistics of representative experiments. Black: Trp8 transfected cells, gray: control cells. Columns from left to right: Trp8 currents at -40 mV (n=12) and +70 mV holding potential (n=12). Trp8 currents in standard bath solution including 120 mM NMDG without sodium (n=7) and with nominal zero calcium ions (n=8) or in the presence of 1mM EGTA with zero divalent cations (n=6). F, representative changes in $[Ca^{2+}]_i$ in Trp8b transfected HEK cells (gray) and controls (black) in the presence or absence of 1mM $[Ca^{2+}]_0$. Inset, relative increase of cytosolic calcium concentration of Trp8b transfected HEK cells, before and after readdition of 1 mM $[Ca^{2+}]_0$ in comparison to control cells.

<u>Figure 4</u>: The C-terminal region of the Trp8 protein binds calmodulin. A, N- and C-terminal fragments of the Trp8 protein used for calmodulin binding studies. B, the Trp8 protein and a truncated Trp8 protein which was in vitro translated after MunI cut of the cDNA, which lacks the C-terminal 32 amino acid residues, were in vitro translated in the presence of ³⁵S-methionine and incubated with calmodulin coupled agarose beads in the presence of 1 mM Ca²⁺ or 2 mM EGTA. C, calmodulin binding to N- and C-terminal fragments of the Trp8protein in the presence of Ca²⁺ (1 mM) or EGTA (2 mM)

Figure 5: Expression pattern of the Trp8 cDNA. A, Northern blots (left panels, Clontech, Palo Alto) were hybridized using a 348 bp NcoI/BamHT fragment of the Trp9 cDNA. The probe hybridizes to mRNA species isolated from the commercial blot, but not to mRNA species isolated from benign prostate hyperplasia (right panel, mRNA isolated from 20 human subjects with benign prostate hyperplasia). B,C, in situ hybridization with biotinylated Trp8 specific oligonucleotides on slides of human tissues. Left column antisense probes, right column sense probes. D, antinsense probes.

Figure 6: Differential expression of Trp8 cDNA in human prostate. A-F, in situ hybridization with prostatic tissues. A, normal prostate, B, primary carcinoma, C, benign hyperplasia, D, rezidive carcinoma, E, prostatic intraepithelial neoplasia, F, lymphnode metastasis of the prostata.

Figure 7: Trp8a cDNA sequence and derived amino acid sequence

Figure 8: A, Trp8b cDNA sequence and derived amino acid sequence

B, cDNA sequence of splice variant 1 (12B1)

C, cDNA sequence of splice variant 2 (17-3)

D, cDNA sequence of splice variant 3 (23A3)

E, cDNA sequence of splice variant 4 (23C3)

Figure 9: A, Trp9 cDNA sequence and derived amino acid sequence B, cDNA sequence of splice variant 15 and derived amino acid sequence.

Figure 10: A, cDNA sequence of Trp10a and derived amino acid sequence, B, cDNA fragment of Trp10a and derived amino acid sequence.

Figure 11: cDNA sequence of Trp10b and derived amino acid sequence.

Figure 12: Expression of Trp8 mRNA in human endometrial cancer or cancer of the uterus. A - D, in situ hybridization with slides of endometrial cancer hybridized with Trp8 antisense (left column) or sense probes as controls (right column). E - F, Trp8 antisense probes hybridized to slides of normal endometrium. It can be clearly seen no hybridization occurs with normal endometrial tissue.

Figure 13: Expression of human Trp9 and Trp10 genes

Northern blots were hybridized using Trp9 (upper panel) or Trp10 (lower panel) specific probes. Expression of the Trp9 cDNA is detectable in many tissues including human prostate and colon as well as in benign prostatic hyperplasia. Expression of Trp10 cDNA is detectable in human prostate of a commercial northern blot (Clontech, right side). This Northern blot contains prostatic tissue collected from 15 human subjects in the range of 14 - 60 years of age. No expression of Trp10 cDNA was detectable in benign prostatic hyperplasia (left side).

Figure 14: Expression of Trp10 transcripts and Trp10-antisense transcripts in human prostate cancer and metastasis of a melanoma. In situ hybridizations of slides hybridized with Trp10-antisense (A-E, K-N) and Trp10 related sense probes (F-J, P-R). It can clearly be seen that both probes detect the same cancer cells indicating that these cancer cells express Trp10 transcripts as well as Trp10-antisense transcripts. S, no Trp10 expression is detectable in benign hyperplasia of the prostate (BPH). O and T, show expression of Trp10 transcripts (O) and Trp10-antisense transcripts (T) in a metastasis of a melanoma in human lung. Melanoma cancer cells express both Trp10 transcripts and Trp10-antisense transcripts.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b or a protein exhibiting biological properties of Trp8a, Trp8b, Trp9, Trp10a or Trp10b and being selected from the group consisting of

- (a) a nucleic acid molecule encoding a protein that comprises the amino acid sequence depicted in Figure 7, 8A, 9,10 or 11;
- (b) a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A, 9,10, or 11;
- (c) a nucleic acid molecule included in DSMZ Deposit no. DSM 13579 (deposit date: 28 June 2000), DSM 13580 (deposit date: 28 June 2000), DSM 13584 (deposit date: 5 July 2000), DSM 13581 (deposit date: 28 June 2000) or DSM(deposit date:....);
- (d) a nucleic acid molecule with hybridizes to a nucleic acid molecule specified in (a) to (c)

(e) a nucleic acid molecule the nucleic acid sequence of which deviates from the nucleic sequences specified in (a) to (d) due to the degeneration of the genetic code; and

(f) a nucleic acid molecule, which represents a fragment, derivative or allelic variation of a nucleic acid sequence specified in (a) to (e).

As used herein, a protein exhibiting biological properties of Trp8a, Trp8b, Trp9,Trp10a or Trp10b is understood to be a protein having at least one of the activities as illustrated in the Examples, below.

As used herein, the term "isolated nucleic acid molecule, includes nucleic acid molecules substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with which it is naturally associated.

In a first embodiment, the invention provides an isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b comprising the amino acid sequence depicted in Figure 7, 8A, 9,10 or 11. The present invention also provides a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A, 9,10 or 11.

The present invention provides not only the generated nucleotide sequence identified in Figure 7, 8A, 9,10 or 11, respectively and the predicted translated amino acid sequence, respectively, but also plasmid DNA containing a Trp8a cDNA deposited with the DSMZ, under DSM 13579, a Trp8b cDNA deposited with the DSMZ, under DSM 13580, a Trp9 cDNA deposited with the DSMZ, under DSM 13581, and a Trp10b cDNA deposited with the DSMZ, under DSM...., respectively. The nucleotide sequence of each deposited Trp-clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by each deposited clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited Trp-encoding DNA, collecting the protein, and determining its sequence.

The nucleic acid molecules of the invention can be both DNA and RNA molecules. Suitable DNA molecules are, for example, genomic or cDNA molecules. It is understood that all

nucleic acid molecules encoding all or a portion of Trp8a, Trp8b, Trp9,Trp10a or Trp10b are also included, as long as they encode a polypeptide with biological activity. The nucleic acid molecules of the invention an be isolated from natural sources or can be synthesized according to know methods.

The present invention also provides nucleic acid molecules which hybridize to the above nucleic acid molecules. As used herein, the term "hybridize, has the meaning of hybridization under conventional hybridization conditions, preferably under stringent conditions as described, for example, in Sambrook et al., Molecular Cloning, A Laboratory Manual 2nd edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. Also contemplated are nucleic acid molecules that hybridize to the Trp nucleic acid molecules at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency), salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°Cin a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 9.2M NaH₂PO₄; 0.02M EDTA, pH7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA, following by washes at 50°C with 1 X SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC). Variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Nucleic acid molecules that hybridize to the molecules of the invention can be isolated, e.g., from genomic or cDNA libraries that were produced from human cell lines or tissues. In order to identify and isolate such nucleic acid molecules the molecules of the invention or parts of these molecules or the reverse complements of these molecules can be used, for example by means of hybridization according to conventional methods (see, e.g., Sambrook et al., supra). As a hybridization probe nucleic acid molecules can be used, for example, that have exactly or basically the nucleotide sequence depicted in Figure 7, 8A, 9,10 or 11, respectively, or parts of these sequences. The fragments used as hybridization probe can be synthetic

fragments that were produced by means of conventional synthetic methods and the sequence of which basically corresponds to the sequence of a nucleic acid molecule of the invention.

The nucleic acid molecules of the present invention also include molecules with sequences that are degenerate as a result of the genetic code.

In a further embodiment, the present invention provides nucleic acid molecules which comprise fragments, derivatives and allelic variants of the nucleic acid molecules described above encoding a protein of the invention. "Fragments, are understood to be parts of the nucleic acid molecules that are long enough to encode one of the described proteins. These fragments comprise nucleic acid molecules specifically hybridizing to transcripts of the nucleic acid molecules of the invention. These nucleic acid molecules can be used, for example, as probes or primers in the diagnostic assay and/or kit described below and, preferably, are oligonucleotides having a length of at least 10, in particular of at least 15 and particularly preferred of at least 50 nucleotides. The nucleic acid molecules and oligonucleotides of the invention can also be used, for example, as primers for a PCR reaction. Examples of particular useful probes (primers) are shown in Tables 1 and 2.

Table 1

Trp8 probes used for in situ hybridization:

Probes (antisense)

- 1.) 5' TCCGCTGCCGGTTGAGATCTTGCC 3'
- 2.) 5' CTTGCTCCATAGGCAGAGAATTAG 3'
- 3.) 5' ATCCTCAGAGCCCCGGGTGTGGAA3'

Controls (sense)

- 1.) 5' GGCAAGATCTCAACCGGCAGCGGA 3'
- 2.) 5' CTAATTCTCTGCCTATGGAGCAAG 3'
- 3.) 5' TTCCACACCCGGGGCTCTGAGGAT 3'

Tabelle 2

Trp10 probes used for the in situ hybridizations shown in Figure 14:

Probes (antisense)

1.) 5' GCTTCCACCCCAAGCTTCACAGGAATAGA 3' (Figure 14 A, 14B)

2.) 5' GGCGATGAAATGCTGGTCTGTGGC 3' (Figure 14C, 14D, 14N, 14S, 14O)

3.) 5' ATCTTCCAGTTCTTGGTGTCTCGG 3' (Figure 14E, 14K)

4.) 5' GCTGCAGTACTCCTGCACCAGGAA 3' (Figure 14L, 14M)

Probes (sense)

1.) 5' TCTATTCCTGTGAAGCTTGGGGTGGAAGC 3' (Figure 14F, 14G)

2.) 5' GCCACAGACCAGCATTTCATCGCC 3' (Figure 14H, 14I, 14T)

3.) 5' CCGAGACACCAAGAACTGGAAGAT 3' (Figure 14J, 14P)

4.) 5' TTCCTGGTGCAGGAGTACTGCAGC 3' (Figure 14Q, 14R)

The term "derivative, in this context means that the sequences of these molecules differ from the sequences of the nucleic acid molecules described above at one or several positions but have a high level of homology to these sequences. Homology hereby means a sequence identity of at least 40%, in particular an identity of at least 60%, preferably of more than 80% and particularly preferred of more than 90%. These proteins encoded by the nucleic acid molecules have a sequence identity to the amino acid sequence depicted in Figure 7, 8A, 9, 10 and 11, respectively, of at least 80%, preferably of 85% and particularly preferred of more than 90%, 97% and 99%. The deviations to the above-described nucleic acid molecules may have been produced by deletion, substitution, insertion or recombination. The definition of the derivatives also includes splice variants, e.g. the splice variants shown in Figures 8B to 8E and 9B.

The nucleic acid molecules that are homologous to the above-described molecules and that represent derivatives of these molecules usually are variations of these molecules that represent modifications having the same biological function. They can be naturally occurring variations, for example sequences from other organisms, or mutations that can either occur naturally or that have been introduced by specific mutagenesis. Furthermore the variations can be synthetically produced sequences. The allelic variants can be either naturally occurring variants or synthetically produced variants or variants produced by recombinant DNA processes.

Generally, by means of conventional molecular biological processes it is possible (see, e.g., Sambrook et al., supra) to introduce different mutations into the nucleic acid molecules of the invention. As a result Trp proteins or Trp related proteins with possibly modified biological properties are synthesized. One possibility is the production of deletion mutants in which nucleic acid molecules are produced by continuous deletions from the 5'- or 3'-terminal of the coding DNA sequence and that lead to the synthesis of proteins that are shortened accordingly. Another possibility is the introduction of single-point mutation at positions where a modification of the amino aid sequence influences, e.g., the ion channel properties or the regulations of the trp-ion channel. By this method muteins can be produced, for example, that possess a modified ion conducting pore, a modified K_m-value or that are no longer subject to the regulation mechanisms that normally exist in the cell, e.g. with regard to allosteric regulation or covalent modification. Such muteins might also be valuable as therapeutically useful antagonists of Trp8a, Trp8b, Trp9,Trp10a or Trp10b, respectively.

For the manipulation in prokaryotic cells by means of genetic engineering the nucleic acid molecules of the invention or parts of these molecules can be introduced into plasmids allowing a mutagenesis or a modification of a sequence by recombination of DNA sequences. By means of conventional methods (cf. Sambrook et al., supra) bases can be exchanged and natural or synthetic sequences can be added. In order to link the DNA fragments with each other adapters or linkers can be added to the fragments. Furthermore, manipulations can be performed that provide suitable cleavage sites or that remove superfluous DNA or cleavage sites. If insertions, deletions or substitutions are possible, in vitro mutagenesis, primer repair, restriction or ligation can be performed. As analysis method usually sequence analysis, restriction analysis and other biochemical or molecular biological methods are used.

The proteins encoded by the various variants of the nucleic acid molecules of the invention show certain common characteristics, such as ion channel activity, molecular weight, immunological reactivity or conformation or physical properties like the electrophoretical mobility, chromatographic behavior, sedimentation coefficients, solubility, spectroscopic properties, stability; pH optimum, temperature optimum.

The invention furthermore relates to vectors containing the nucleic acid molecules of the invention. Preferably, they are plasmids, cosmids, viruses, bacteriophages and other vectors

usually used in the field of genetic engineering. Vectors suitable for use in the present invention include, but are not limited to the T7-based expression vector for expression in mammalian cells and baculovirus-derived vectors for expression in insect cells. Preferably, the nucleic acid molecule of the invention is operatively linked to the regulatory elements in the recombinant vector of the invention that guarantee the transcription and synthesis of an RNA in prokryotic and/or eukaryotic cells that can be translated. The nucleotide sequence to be transcribed can be operably linked to a promoter like a T7, metallothionein I or polyhedrin promoter.

In a further embodiment, the present invention relates to recombinant host cells transiently or stable containing the nucleic acid molecules or vectors or the invention. A host cell is understood to be an organism that is capable to take up *in vitro* recombinant DNA and, if the case may be, to synthesize the proteins encoded by the nucleic acid molecules of the invention. Preferably, these cells are prokaryotic or eukaryotic cells, for example mammalian cells, bacterial cells, insect cells or yeast cells. The host cells of the invention are preferably characterized by the fact that the introduced nucleic acid molecule of the invention either is heterologous with regard to the transformed cell, i.e. that it does not naturally occur in these cells, or is localized at a place in the genome different from that of the corresponding naturally occurring sequence.

A further embodiment of the invention relates to isolated proteins exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b and being encoded by the nucleic acid molecules of the invention, as well as to methods for their production, whereby, e.g., a host cell of the invention is cultivated under conditions allowing the synthesis of the protein and the protein is subsequently isolated from the cultivated cells and/or the culture medium. Isolation and purification of the recombinantly produced proteins may be carried out by conventional means including preparative chromatography and affinity and immunological separations involving affinity with an anti-Trp8a-, anti-Trp9-,anti-Trp10a- or anti-Trp10b-antibody, respectively.

As used herein, the term "isolated protein, includes proteins substantially free of other proteins, nucleic acids, lipids, carbohydrates or other materials with which it is naturally associated. Such proteins however not only comprise recombinantly produced proteins but include isolated naturally occurring proteins, synthetically produced proteins, or proteins

produced by a combination of these methods. Means for preparing such proteins are well understood in the art. The Trp proteins are preferably in a substantially purified form. A recombinantly produced version of a human prostate carcinoma associated protein Trp8a, Trp8b, Trp9,Trp10a or Trp10b protein, including the secreted protein, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67, 31-40 (1988).

In a further preferred embodiment, the present invention relates to an antisense RNA sequence characterised that it is complementary to an mRNA transcribed from a nucleic acid molecule of the present invention or a part thereof and can selectively bind to said mRNA, said sequence being capable of inhibiting the synthesis of the protein encoded by said nucleic acid molecules, and a ribozyme characterised in that it is complementary to an mRNA transcribed from a nucleic acid molecule of the present invention or a part thereof and can selectively bind to and cleave said mRNA, thus inhibiting the synthesis of the proteins encoded by said nucleic acid molecules. Riboyzmes which are composed of a single RNA chain are RNA enzymes, i.e. catalytic RNAs, which can intermolecularly cleave a target RNA, for example the mRNA transcribed from one of the Trp genes. It is now possible to construct ribozymes which are able to cleave the target RNA at a specific site by following the strategies described in the literature. (see, e.g., Tanner et al., in: Antisense Research and Applications, CRC Press Inc. (1993), 415-426). The two main requirements for such ribozymes are the catalytic domain and regions which are complementary to the target RNA and which allow them to bind to its substrate, which is a prerequisite for cleavage. Said complementary sequences, i.e., the antisense RNA or ribozyme, are useful for repression of Trp8a-, Trp8b, Trp9-, Trp10a- and Trp10b-expression, respectively, i.e. in the case of the treatment of a prostate cancer or endometrial cancer (carcinoma of the uterus). Preferably, the antisense RNA and ribozyme of the invention are complementary to the coding region. The person skilled in the art provided with the sequences of the nucleic acid molecules of the present invention will be in a position to produce and utilise the above described antisense RNAs or ribozymes. The region of the antisense RNA and ribozyme, respectively, which shows complementarity to the mRNA transcribed from the nucleic acid molecules of the present invention preferably has a length of at least 10, in particular of at least 15 and particularly preferred of at least 50 nucleotides.

In still a further embodiment, the present invention relates to inhibitors of Trp8a, Trp8b, Trp9, Trp10a and Trp10b, respectively, which fulfill a similar purpose as the antisense RNAs or

ribozymes mentioned above, i.e. reduction or elimination of biologically active Trp8a, Trp8b, Trp9, Trp10a or Trp10b molecules. Such inhibitors can be, for instance, structural analogues of the corresponding protein that act as antagonists. In addition, such inhibitors comprise molecules identified by the use of the recombinantly produced proteins, e.g. the recombinantly produces protein can be used to screen for and identify inhibitors, for example, by exploiting the capability of potential inhibitors to bind to the protein under appropriate conditions. The inhibitors can, for example, be identified by preparing a test mixture wherein the inhibitor candidate is incubated with Trp8a, Trp8b, Trp9, Trp10a or Trp10b, respectively, under appropriate conditions that allow Trp8a, Trp8b, Trp9, Trp10a or Trp10b to be in a native conformation. Such an in vitro test system can be established according to methods well known in the art. Inhibitors can be identified, for example, by first screening for either synthetic or naturally occurring molecules that bind to the recombinantly produced Trp protein and then, in a second step, by testing those selected molecules in cellular assays for inhibition of the Trp protein, as reflected by inhibition of at least one of the biological activities as described in the examples, below. Such screening for molecules that bind Trp8a, Trp8b, Trp9, Trp10a or Trp10b could easily performed on a large scale, e.g. by screening candidate molecules from libraries of synthetic and/or natural molecules. Such an inhibitor is, e.g., a synthetic organic chemical, a natural fermentation product, a substance extracted from a microorganism, plant or animal, or a peptide. Additional examples of inhibitors are specific antibodies, preferably monoclonal antibodies. Moreover, the nucleic sequences of the invention and the encoded proteins can be used to identify further factors involved in tumor development and progression. In this context it should be emphasized that the modulation of the calcium channel of a member of the trp family can result in the stimulation of the immune response of T lymphocytes leading to proliferation of the T lymphocytes. The proteins of the invention can, e.g., be used to identify further (unrelated) proteins which are associated with the tumor using screening methods based on protein/protein interactions, e.g. the two-hybridsystem Fields, S. and Song, O. (1989) Nature (340): 245-246.

The present invention also provides a method for diagnosing a prostate carcinoma which comprises contacting a target sample suspected to contain the protein Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA with a reagent which reacts with Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA and detecting Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA.

It has been found that carcinoma cells of placenta (chorion carcinoma), lung and prostate express Trp10 transcripts as well as Trp10 antisense transcripts and transcripts being in part complementary to Trp10 antisense transcripts. Accordingly, the present invention also provides a method for diagnosing a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense RNA.

When the target is mRNA (or antisense RNA), the reagent is typically a nucleic acid probe or a primer for PCR. The person skilled in the art is in a position to design suitable nucleic acids probes based on the information as regards the nucleotide sequence of Trp8a, Trp8b, Trp10a or Trp10b as depicted in figure 7, 8a, 10 and 11, respectively, or tables 1 and 2, above. When the target is the protein, the reagent is typically an antibody probe. The term "antibody", preferably, relates to antibodies which consist essentially of pooled monoclonal antibodies with different epitopic specifities, as well as distinct monoclonal antibody preparations. Monoclonal antibodies are made from an antigen containing fragments of the proteins of the invention by methods well known to those skilled in the art (see, e.g., Köhler et al., Nature 256 (1975), 495). As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab') 2 fragments) which are capable of specifically binding to protein. Fab and f(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24: 316-325 (1983)). Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimerical, single chain, and humanized antibodies. The target cellular component, i.e. Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts, e.g., in biological fluids or tissues, may be detected directly in situ, e.g. by in situ hybridization (e.g., according to the examples, below) or it may be isolated from other cell components by common methods known to those skilled in the art before contacting with a probe. Detection methods include Northern blot analysis, RNase protection, in situ methods, e.g. in situ hybridization, in vitro amplification methods (PCR, LCR, QRNA replicase or RNA-transcription/amplification (TAS, 3SR), reverse dot blot disclosed in EP-B1 O 237 362)), immunoassays, Western blot and other detection assays that are known to those skilled in the art.

Products obtained by in vitro amplification can be detected according to established methods, e.g. by separating the products on agarose gels and by subsequent staining with ethidium bromide. Alternatively, the amplified products can be detected by using labeled primers for amplification or labeled dNTPs.

The probes can be detectable labeled, for example, with a radioisotope, a bioluminescent, compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

Expression of Trp8a, Trp8b, Trp10a and Trp10b, respectively, in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101 (1985), 976-985; Jalkanen et al., J. Cell. Biol. 105 (1987), 3087-3096; Sobol et al. Clin. Immunpathol. 24 (1982), 139-144; Sobol et al., Cancer 65 (1985), 2005-2010). Other antibody based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125L 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium rhodamine, and biotin. In addition to assaying Trp8a, Trp8b, Trp 10a or Trp10b levels in a biological sample, the protein can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by Xradiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ¹³¹I, ¹¹²In, ⁹⁹mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99 mTc. The labeled antibody or antibody fragment will then preferentially accumulate at he location of cells which contain the specific protein. In

vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments". (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B.A. Rhodes, eds., Masson Publishing Inc. (1982)).

The marker Trp8a and Trp8b is also useful for prognosis, for monitoring the progression of the tumor and the diagnostic evaluation of the degree of malignancy of a prostate tumor (grading and staging), e.g. by using in situ hybridization: In a primary carcinoma Trp8 is expressed in about 2 to 10% of carcinoma cells, in a rezidive carcinoma in about 10 to 60% of cells and in metastases in about 60 to 90% of cells.

The present invention also relates to a method for diagnosing endometrial cancer (cancer of the uterus) which comprises contacting a target sample suspected to contain the protein Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA with a reagent which reacts with Trp8a and/or Trp8b or the encoding mRNA and detecting Trp8a and/or Trp8b encoding mRNA. As regards particular embodiments of this method reference is made to the particular embodiments of the method of diagnosing a prostate cancer outlined above.

For evaluating whether the concentration of Trp8a, Trp8b, Trp10a or Trp10b or the concentration of Trp8a, Trp8b, Trp10a or Trp10b encoding mRNA is normal or increased, thus indicative for the presence of a malignant tumor, the measured concentration is compared with the concentration in a normal tissue, preferably by using the ratio of Trp8a:Trp9, Trp8b:Trp9 or Trp10(a or b)/Trp9 for quantification.

Since the prostate carcinoma forms its own basement membrane when growing invasively, it can be concluded that only cells expressing Trp8 and Trp10 are involved in this phenomenon. Thus, it can be concluded that by inhibiting the expression and/or activity of these proteins an effective therapy of cancers like PCA is provided.

Thus, the present invention also relates to a pharmaceutical composition containing a reagent which decreases or inhibits Trp8a, Trp8b, Trp10a and/or Trp10b expression or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b, and a method for preventing, treating, or ameliorating a prostate tumor, endometrial cancer (uterine carcinoma) tumor, a chorion carcinoma, cancer of the lung or melanoma, which comprises administering to a mammalian subject a

therapeutically effective amount of a reagent which decreases or inhibits Trp8a, Trp8b, Trp10a and/or Trp10b expression or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b. Examples of such reagents are the above described antisense RNAs, ribozymes or inhibitors, e.g. specific antibodies. Furthermore, peptides, which inhibit or modulate the biological function of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b may be useful as therapeutical reagents. For example, these peptides can be obtained by screening combina torial phage display libraries (Cosmix, Braunschweig, Germany) as described by Rottgen, P. and Collins, J. (Gene (1995) 164 (2): 243-250). Furthermore, antigenic epitopes of the Trp8 and Trp10 proteins can be identified by the expression of recombinant Trp8 and Trp10 epitope libraries in E. coli (Marquart, A. & Flockerzi, V., FEBS Lett. 407 (1997), 137-140; Trost, C., et al., FEBS Lett. 451 (1999) 257-263 and the consecutive screening of these libraries with serum of patients with cancer of the prostate or of the endometrium. Those Trp8 and Trp10 epitopes which are immunogenic and which lead to the formation of antibodies in the serum of the patients can be then be used as Trp8 or Trp10 derived peptide vaccines for immune inventions against cancer cells which express Trp8 or Trp10. Alternatively to the E. coli expression system, Trp8 or Trp10 or epitopes of Trp8 and Trp10 can be expressed in mammalian cell lines such as human embryonic kidney (Hek 293) cells (American Type Culture Collection, ATCC CRL 1573).

Finally, compounds useful for therapy of the above described diseases comprise compounds which act as antagonists or agonists on the ion channels Trp8, Trp9 and Trp10. It could be shown that Trp8 is a highly calcium selective ion channel which in the presence of monovalent (namely sodium) and divalent ions (namely calcium) is only permeable for calcium ions (see Example 4, below, and Figures 3A, C, E). Under physiological conditions, Trp8 is a calcium selective channel exhibiting large inward currents. This very large conductance of Trp8 channels (as wells as Trp9 and Trp10a/b channels) is useful to establish systems for screening pharmacological compounds interacting with Trp-channels including high throughput screening systems. Useful high throughput screening systems are well known to the person skilled in the art and include, e.g., the use of cell lines stably or transiently transfected with DNA sequences encoding Trp8, Trp9 and Trp10 channels in assays to detect calcium signaling in biological systems. Such systems include assays based on Ca-sensitive dyes such as aequorin, apoaequorin, Fura-2, Fluo-3 and Indo-1.

Accordingly, the present invention also relates to a method for identifying compounds which act as agonists or antagonists on the ion channels Trp8, Trp9 and/or Trp10, said method comprising contacting a test compound with the ion channel Trp8, Trp9 and/or Trp10, preferably by using a system based on cells stably or transiently transfected with DNA sequences encoding Trp8, Trp9 and/or Trp10, and determining whether said test compound affects the calcium uptake.

For administration the above described reagents are preferably combined with suitable pharmaceutical carriers. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Such carriers can be formulated by conventional methods and can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g. by intravenous, intraperetoneal, subcutaneous, intramuscular, topical or intradermal administration. The route of administration, of course, depends on the nature of the tumor and the kind of compound contained in the pharmaceutical composition. The dosage regimen will be determined by the attending physician and other clinical factors. As is well known in the medical arts, dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind and stage of the tumor, general health and other drugs being administered concurrently.

The delivery of the antisense RNAs or ribozymes of the invention can be achieved by direct application or, preferably, by using a recombinant expression vector such as a chimeric virus containing these compounds or a colloidal dispersion system. By delivering these nucleic acids to the desired target, the intracellular expression of Trp8a, Trp8b, Trp10a and/or Trp10b and, thus, the level of Trp8a, Trp8b, Trp10a and/or Trp10b can be decreased resulting in the inhibition of the negative effects of Trp8a, Trp8b, Trp10a and/or Trp10b, e.g. as regards the metastasis formation of PCA.

Direct application to the target site can be performed, e.g., by ballistic delivery, as a colloidal dispersion system or by catheter to a site in artery. The colloidal dispersion systems which can be used for delivery of the above nucleic, acids include macromolecule complexes, nanocapsules, microspheres, beads and lipid-based systems including oil-in-water emulsions

(mixed), micelles, liposomes and lipoplexes, The preferred colloidal system is a liposome. The composition of the liposome is usually a combination of phospholipids and steroids, especially cholesterol. The skilled person is in a position to select such liposomes which are suitable for the delivery of the desired nucleic acid molecule. Organ-specific or cell-specific liposomes can be used in order to achieve delivery only to the desired tumor. The targeting of liposomes can be carried out by the person skilled in the art by applying commonly known methods. This targeting includes passive targeting (utilizing the natural tendency of the liposomes to distribute to cells of the RES in organs which contain sinusoidal capillaries) or active targeting (for example by coupling the liposome to a specific ligand, e.g., an antibody, a receptor, sugar, glycolipid, protein etc., by well known methods). In the present invention monoclonal antibodies are preferably used to target liposomes to specific tumors via specific cell-surface ligands.

Preferred recombinant vectors useful for gene therapy are viral vectors, e.g. adenovirus, herpes virus, vaccinia, or, more preferably, an RNA virus such as a Retrovirus. Even more preferably, the retroviral vector is a derivative of a murine or avian retrovirus. Examples of such retroviral vectors which can be used in the present invention are: Moloney murine leukemia virus (MoMuLV). Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV) and Rous sarcoma virus (RSV). Most preferably, a non-human primate retroviral vector is employed, such as the gibbon ape leukemia virus (GaLV), providing a broader host range compared to murine vectors. Since recombinant retroviruses are defective, assistance is required in order to produce infectious particles. Such assistance can be provided, e.g., by using helper cell lines that contain plasmids encoding all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR. Suitable helper cell lines are well known to those skilled in the art. Said vectors can additionally contain a gene encoding a selectable marker so that the transduced cells can be identified. Moreover, the retroviral vectors can be modified in such a way that they become target specific. This can be achieved, e.g., by inserting a polynucleotide encoding a sugar, a glycolipid, or a protein, preferably an antibody. Those skilled in the art know additional methods for generating target specific vectors. Further suitable vectors and methods for in vitro- or in vivo-gene therapy are described in the literature and are known to the persons skilled in the art; see, e.g., WO 94/29469 or WO 97/00957.

In order to achieve expression only in the target organ, i.e. tumor to be treated, the nucleic acids encoding, e.g. an antisense RNA or ribozyme can also be operably linked to a tissue specific promoter and used for gene therapy. Such promoters are well known to those skilled in the art (see e.g. Zimmermann et al., (1994) Neuron 12, 11-24; Vidal et al.; (1990) EMBO J. 9, 833-840; Mayford et al., (1995), Cell 81, 891-904; Pinkert et al., (1987) Genes & Dev. 1, 268-76).

For use in the diagnostic research discussed above, kits are also provided by the present invention. Such kits are useful for the detection of a target cellular component, which is Trp8a, Trp8b, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts, wherein the presence or an increased concentration of Trp8a, Trp8b, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts is indicative for a prostate tumor, endometrial cancer, melanoma, chorion carcinoma or cancer of the lung, said kit comprising a probe for detection of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b or, alternatively, Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a/b antisense transcripts. The probe can be detectably labeled. Such probe may be a specific antibody or specific oligonucleotide. In a preferred embodiment, said kit contains an anti-Trp8a-, anti-Trp8b-, anti-Trp9-, anti-Trp10a-and/or anti-Trp10b-antibody and allows said diagnosis, e.g., by ELISA and contains the antibody bound to a solid support, for example, a polystyrene microtiter dish or nitrocellulose paper, using techniques known in the art. Alternatively, said kits are based on a RIA and contain said antibody marked with a radioactive isotope. In a preferred embodiment of the kit of the invention the antibody is labeled with enzymes, fluorescent compounds, luminescent compounds, ferromagnetic probes or radioactive compounds. The kit of the invention may comprise one or more containers filled with, for example, one or more probes of the invention. Associated with container (s) of the kit can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, us or sale for human administration.

EXAMPLES

The following Examples are intended to illustrate, but not to limit the invention. While such Examples are typical of those that might be used, other methods known to those skilled in the art may alternatively be utilized.

Example 1: Materials and Methods

(A) Isolation of cDNA clones and Northern blot analysis

Total RNA was isolated from human placenta an prostate using standard techniques. Isolation of mRNA was performed with poly (A)⁺RNA - spin columns (New England Biolabs, Beverly, USA) according to the instructions of the manufacturer. Poly (a) ⁺RNA was reverse transcribed using the cDNA choice system (Gibco-BRL, Rockville, USA) and subcloned in λ-Zap phages (Stratagene, La Jolla, USA). An human expressed sequence tag (GenBank accession number 1404042) was used to screen an oligo d(T) primed human placenta cDNA library. Several cDNA clones were identified and isolated. Additional cDNA clones were isolated from two specifically primed cDNA libraries using primers 5'-gca tag gaa ggg aca ggt gg-3' and 5'-gag agt cga ggt cag tgg tcc-3'.

cDNA clones were sequenced using a thermocycler (PE Applied Biosystems, USA) and Thermo Sequenase (Amersham Pharmacia Biotech Europe, Freiburg, Germany). DNA sequences were analyzed with an automated sequencer (Licor, Linccoln, USA).

For Northern blot analysis 5 μg human poly (A)⁺ RNA from human placenta or prostate were separated by electrophoresis on 0.8 % agarose gels. Poly (A)⁺ RNA was transferred to Hybond N nylon membranes (Amersham Pharmacia Biotech Europe, Freiburg, Germany). The membranes were hyridized in the presence of 50 % formamide at 42°C over night. DNA probes were labelled using [α³²P]dCTP and the "ready prime, labelling kit (Amersham Pharmacia Biotech Europe, Freiburg, Germany). Commercial Northern blots were hybridized according to the distributors instructions (Clontech, Paolo Alto, USA).

(B) Construction of expression plasmids and transfection of HEK 293 cells

Lipofections were carried out with the recombinant dicistronic eucaryotic expression plasmid pdiTRP8 containing the cDNA of Trp8b under the control of the chicken β-actin promotor followed by an internal ribosome entry side (IRES) and the cDNA of the green fluorescent protein (GFP). To obtain pdiTRP8 carrying the entire protein coding regions of TRP8b and

the GFP (Prasher, D.C. et al. (1992), Gene 111, 229-233), the 5' and 3'-untranslated sequences of the TRP8b cDNA were removed, the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was introduced immediately 5' of the translation initiation codon and the resulting cDNA was subcloned into the pCAGGS vector (Niwa, H., Yamamura, K. and Miyazaki, J (1991), Gene 8, 193-199) downstream of the chicken β-actin promotor. The IRES derived from encephalmyocarditis virus (Kim, D.G., Kang, H.M., Jang, S.K. and Shin H.S. (1992) Mol.Cell.Biol. 12, 3636-3643) followed by the GFP cDNA containing a Ser65Thr mutation (Heim, R., Cubitt, A.B., Tsien, R.Y. (1995) Nature 373, 663-664) was then cloned 3' to the TRP8b cDNA. The IRES sequence allows the simultaneous translation of TRP8b and GFP from one transcript. Thus, transfected cells can be detected unequivocally by the development of green fluorescence.

For monitoring of the intracellular Ca²⁺ concentration human embryonic kidney (HEK 293) cells were cotransfected with the pcDNA3-TRP8b vector and the pcDNA3-GFPvector in a molar ratio of 4:1 in the presence of lipofectamine (Quiagen, Hilden, Germany). To obtain pcDNA3-TRP8b the entire protein coding region of TRP8b including the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was subcloned into the pcDNA3 vector (Invitrogen, Groningen, Netherlands). Calcium monitoring and patch clamp experiments were carried out two days and one day after transfection, respectively.

(C) Chromosomal localization of the Trp8 gene

The chromosomal localization of the human TRP8 gene was performed using NIGMS somatic hybrid mapping panel No.2 (Coriell Institute, Camden, NJ, USA) previously described (Drwinga, H.L., Toji, L.H., Kim, C.H., Greene, A.E., Mulivor, R.A. (1993) Genomics 16, 311-314; Dubois, B.L. and Naylor, S.L. (1993) Genomics 16, 315-319).

(D) In Vitro Translation, glutathione - sepharose and calmodulin agarose binding assay N- and C-terminal Trp8-fragments were subcloned into the pGEX-4T2 vector (Amersham Pharmacia Europe, Freiburg, Germany) resulting in glutathione-S-transferase (GST)-Trp8 fusion constructs (Fig. 4). The GST-TRP8-fusion proteins were expressed in E. coli BL 21 cells and purified using glutathione - sepharose beads (Amersham Pharmacia Biotech Europe, Freiburg, Germany).

In vitro translation of human Trp8 cDNA and Xenopus laevis calmodulin cDNA (Davis, T.N. and Thorner, J. Proc.Natl.Acad.Sci. USA 86, 7909-7913.) was performed in the presence of ³⁵S-methionine using the TNT coupled transcription/translation kit (Promega, Madison, USA). Translation products were purified by gel fliltration (Sephadex G50, Amersham Pharmacia Biotech Europe, Freiburg, Germany) and equal amounts of ³⁵S labeled probes were incubated for 2 h with glutathione beads bound to GST - Trp8 or calmodulin - agarose (Calbiochem) in 50 mM Tris-HCl, pH 7.4, 0.1 % Triton X-100, 150 mM NaCl in the presence of 1 mM Ca²⁺ or 2 mM EGTA. After three washes, bound proteins were eluted with SDS sample buffer, fractionated by SDS-PAGE and ³⁵S labeled proteins were detected using a Phosphor Imager (Fujifilm, Tokyo, Japan).

(E) Calcium measurements

The intracellular Ca²⁺ concentration ([Ca²⁺]_i) was determined by dual wavelength fura-2 fluorescence ratio measurements (Tsien, R.Y. (1988) Trends Neurosci. 11, 419-424) using a digital imaging system (T.I.L.L. Photonics, Planegg, Germany). HEK cells were grown in minimal essential medium in the presence of 10 % fetal calf serum and cotransfected with the pcDNA3-TRP8b vector and the pcDNA3-GFPvector as described above (B). Transfected cells were detected by development of green fluorescence. The cells were loaded with 4μM fura-2/AM (Molecular Probes, Oregon, USA) for one hour. After loading the cells were rinsed 3 times with buffer B1 (10 mM Hepes, 115 mM NaCl, 2 mM MgCl₂, 5mM KCl, pH 7.4) and the [Ca²⁺]_i was calculated from the fluorescence ratios obtained at 340 and 380 nm excitation wavelengths as described (Garcia, D.E., Cavalié, A. and Lux, H.D. (1994) J. Neurosci 14, 545-553).

(F) Electrophysiological recordings

HEK cells were transfected with the eucaryotic expression plasmid pdiTRP8 described in (B) and electrophysiolocigal recordings were carried out one day after transfection. Single cells were voltage clamped in the whole cell mode of the patch clamp technique as described (Hamill, O.P., Marty, A., Neher, E., Sakmann, B. and Sigworth, F.J. (1981) Pflügers Arch. 391, 85-100; Philipp, S., Cavalié, A., Freichel, M., Wissenbach, U., Zimmer, S., Trost, C., Marquart, A., Murakami, M. and Flockerzi, V. (1996) EMBO J. 6166-6171). The pipette solution contained contained (mM): 140 aspartic acid, 10 EGTA, 10 NaCl, 1 MgCl2, 10 Hepes (pH 7.2 with CsOH) or 125 CsCl, 10 EGTA, 4 CaCl₂ 10 Hepes (pH 7,2 with CsOH). The bath solution contained (mM): 100 NaCl, 10 CsCl, 2 MgCl₂, 50 mannitol, 10 glucose, 20

Hepes (pH 7,4 with CsOH) and 2 CaCl₂, or no added CaCl₂ (-Ca²⁺ solution). Divalent free bath solution contained (mM): 110 N-methyl-D-glucamine (NMDG). Whole cell currents were recorded during 100 msec voltage ramps from -100 to +100 mV at varying holding potentials.

(G) In Situ Hybridization

In situ hybridizations were carried out using formalin fixed tissue slices of 6 - 8 µM thickness. The slices were hydrated and incubated in the presence of PBS buffer including 10 µg / ml proteinase K (Roche Diagnostics, Mannheim, Germany) for 0.5 h. The slices were hybridized at 37°C using biotinylated deoxy-oligonucleotides (0.5 pmol / µl) in the presence of 33 % formamide for 12 h. Furthermore the slices were several times rinsed with 2 x SSC and incubated at 25°C for 0.5 h with avidin / biotinylated horse raddish peroxidase complex (ABC, DAKO, Santa Barbara, USA). After several washes with PBS buffer the slices were incubated in the presence of biotinylated tyramid and peroxide (0.15 % w/v) for 10 min, rinsed with PBS buffer and additionally incubated with ABC complex for 0.5 h. The slices were washed with PBS buffer and incubated in the presence of DAB solution (diaminobenzidine (50μg / ml), 50 mM Tris/EDTA buffer pH 8.4, 0.15 % H₂O₂ in N,N dimethyl-formamide; Merck, Darmstadt, Germany), The detection was stopped after 4 minutes by incubating the slides in water. Tyramid was biotinylated by incubating NHS-LC Biotin (sulfosuccinimidyl-6-(biotinimid)-hexanoat), 2.5 mg/ml; Pierce, Rockford, USA) and tyramin-HCl (0.75 mg / ml, Sigma) in 25 mM borate buffer pH 8.5 for 12 h. The tyramid solution was diluted 1 - 5: 1000 in PBS buffer.

(H) GenBank accession numbers: TRP8a, Aj243500; TRP8b Aj243501

Example 2: Expression of TRP8 transcripts

In search of proteins distantly related to the TRP family of ion channels, an human expressed sequence tag (EST, GenBank accession number 1404042) was identified in the GenBank database using BLAST programms (at the National Center for Biotechnology Information (NCBI); Altschul, S.F., Gish, W., Miller, W., Myers, E.W. and Lipman, D.J.J. (1990) Mol. Biol. 5, 403-410) being slightly homologous to the VR1 gene. Several human placenta cDNA libraries were constructed and screeened with this EST DNA as probe. Several full length

cDNA clones were identified and isolated. The full length cDNA clones encoded two putative proteins differing in three amino acids and were termed Trp8a and Trp8b (Fig. 1c, 2a, 7 and 8A). This finding was reproduced by isolating cDNA clones from two cDNA libraries constructed from two individual placentas. The derived protein sequence(s) comprises six transmembrane domains, a characteristic overall feature of trp channels and related proteins (Fig.: 1b). The sequence is closely related to the meanwhile published calcium uptake transport protein 1 (CaT1), isolated from rat intestine (Peng, J.B., Chen, X.Z., Berger, U.V., Vassilev, P.M., Tsukaguchi, H., Brown, E.M. and Hediger M.A.(1999) J Biol Chem. 6;274, 22739-22746) and to the epithelial calcium uptake channel (ECaC) isolated from rabbit kidney (Hoenderop, J.G., van der Kemp, A.W., Hartog, A., van de Graaf, S.F., van Os, C.H., Willems, P.H. and Bindels, R.J. (1999) J Biol Chem. 26;274, 8375-8378). Expression of Trp8a/b transcripts are detectable in human placenta, pancreas and prostate (Fig.: 5) and the size of the Northern signal (3.0 kb) corresponds with the size of the isolated full length cDNAs. In addition, a shorter transcript of 1.8 kb, probably a splice variant, is detectable in human testis. The Trp8 mRNA is not expressed in small intestine or colon (Fig.: 5) implicating that Trp8 is not the human ortholog of the rat CaT1 or rabbit ECaC proteins. To investigate whether there are other related sequences Trp8a/b derived primers (UW241, 5'-TAT GAG GGT TCA GAC TGC-3' and UW242, 5'-CAA AGT AGA TGA GGT TGC-3') were used to amplify a 105 bp fragment from human genomic DNA being 95% identical on the nucleotide level to the Trp8 sequence (data not shown). This indicates the existence of several similar sequences in humans at least at the genomic level.

Example 3: Two variants of the Trp8 protein (Trp8a and Trp8b) arise by polymorphism

Two variants of the Trp8 cDNA were isolated from human placenta (Fig.: 2A, 7 and 8A) which encoded two proteins which differ in three amino acids and were termed Trp8a and Trp8b. Trp8a/b specific primers were designed to amplify a DNA fragment of 458 bp of the Trp8 gene from genomic DNA isolated from human T-lymphocytes (primer pair: UW243, 5'-CAC CAT GTG CTG CAT CTA CC-3' and UW244, 5'-CAA TGA CAG TCA CCA GCT CC-3'). The amplification product contains a part of the sequence where the derived protein sequence of Trp8a comprises the amino acid valine and the Trp8b sequence methionine as well as a silent base pair exchange (g versus a) and an intron of 303bp (Fig.: 2.A, B). Both variants of the Trp8 genes (a,b) were amplified from genomic DNA in equal amounts indicating the existence of both variants in the human genome and therefore being not the

result of RNA editing (Fig.: 2B). The Trp8a gene can be distinguished from the Trp8b gene by cutting the genomic fragment of 458bp with the restriction enzyme Bsp1286I (Fig. 2B). Using human genomic DNA isolated from blood of twelve human subjects as template, the 458bp fragment was amplified and restricted with BSP1286I. In eleven of the tested subjects only the Trp8b gene is detectable, while one subject (7) contains Trp8a and Trp8b genes (Fig.: 2D). These implicates that the two Trp8 variants arise by polymorphism and do not represent individual genes. Using Trp8 specific primers and chromosomal DNA as template, the Trp8 locus is detectable on chromosome 7 (Fig.: 2C).

Example 4: Trp8b is a calcium permeable channel

The protein coding sequence of the Trp8b cDNA was subcloned into pcDNA3 vector (Invitrogen, Groningen, Netherlands) under the control of the cytomegalovirus promotor (CMV). Human embryonic kidney (HEK 293) cells were cotransfected with the Trp8b pcDNA3 construct (pcDNA3-Trp8b vector) and the pcDNA3-GFPvector encoding the green fluorescent protein (GFP) in 4:1 ratio. The Trp8b cDNA and the cDNA of the reporter, GFP, was transiently expressed in human embryonic kidney (HEK 293) cells. The intracellular Ca²⁺ concentration ([Ca²⁺]_i) and changes of [Ca²⁺]_i were determined by dual wavelength fura-2 fluorescence ratio measurements (Fig.: 3F) in cotransfected cells which were identified by the green fluorescence of the reporter gene GFP.

Dual wavelength fura-2 fluorescence ratio measurement is a standard procedure (e.g. in: An introduction of Molecular Neurobiology (ed. Hall, Z.W.)Sinauer Associates, Sunderland, USA (1992)) using fura-2, which is a fluorescent Ca²⁺ sensitive dye and which was designed by R.Y.Tsien (e.g. Trends Neurosci. 11, 419-424 (1988) based upon the structure of EGTA. Its fluorescence emission spectrum is altered by binding to Ca²⁺ in the physiological concentration range. In the absence of Ca²⁺, fura-2 fluoresces most strongly at an excitation wavelength of 385 nm; when it binds Ca²⁺, the most effective excitation wavelength shifts to 345 nm. This property is used to measure local Ca²⁺ concentrations within cells. Cells can be loaded with fura-2 esters (e.g. fura-2AM) that diffuse across cell membranes and are hydrolyzed to active fura-2 by cytosolic esterases.

In the presence of 1mM Ca²⁺, Trp8 expressing cells typically contained more than 300 nM cytosolic Ca²⁺, while non transfected controls contained less than 100 nM Ca²⁺ ions (Fig. 3F).

When Trp8b transfected cells were incubated without extracellular Ca²⁺, the intracellular Ca²⁺ concentration ([Ca²⁺]_i) decreased to levels comparable to non transfected cells. Readdition of 1mM Ca²⁺ to the bath resulted in significant increase of the cytosolic [Ca²⁺] in Trp8b transfected cells, but not in controls (Fig.: 3F). After readdition of Ca²⁺ ions to the bath solution, the cytosolic Ca²⁺ concentration remains on a high steady state level in the Trp8b transfected cells.

Example 5: Trp8 expressing cells show calcium selective inward currents

To characterize in detail the electrophysiological properties of TRP8, TRP8 and GFP were coexpressed in HEK293 cells using the dicistronic expression vector pdiTRP8 and measured currents using the patch clamp technique in the whole cell mode (Hamill, O.P., Marty, A., Neher, E., Sakmann, B. and Sigworth, F.J. (1981) Pflugers Arch., 391, 85-100).

The eucaryotic expression plasmid pdiTRP8 contains the cDNA of Trp8b under the control of the chicken β-actin promotor followed by an internal ribosome entry side (IRES) and the cDNA of the green fluorescent protein (GFP). To obtain pdiTRP8 carrying the entire protein coding regions of TRP8b and the GFP (Prasher, D.C. et al. (1992), Gene 111, 229-233), the 5'and 3'-untranslated sequences of the TRP8b cDNA were removed, the consensus sequence for initiation of translation in vertebrates (Kozak, M. (1987) Nucleic Acids Research15, 8125-8148) was introduced immediately 5'of the translation initiation codon and the resulting cDNA was subcloned into the pCAGGS vector (Niwa, H., Yamamura, K. and Miyazaki, J (1991), Gene 8, 193-199) downstream of the chicken β-actin promotor. The IRES derived from encephalmyocarditis virus (Kim, D.G., Kang, H.M., Jang, S.K. and Shin H.S. (1992) Mol.Cell.Biol. 12, 3636-3643) followed by the GFP cDNA containing a Ser65Thr mutation (Heim, R., Cubitt, A.B., Tsien, R.Y. (1995) Nature 373, 663-664) was then cloned 3' to the TRP8b cDNA. The IRES sequence allows the simultaneous translation of TRP8b and GFP from one transcript. Thus, transfected cells can be detected unequivocally by the development of green fluorescence.

In the presence of 2 mM external calcium, Trp8b transfected HEK cells show inwardly rectifying currents, the size of which depends on the level of intracellular calcium and the electrochemical driving force. The resting membrane potential was held either at -40 mV, or, to lower the driving force for calcium influx in between pulses, at +70 mV. Current traces

were recorded in response to voltage ramps from -100 to +100 mV, that were applied every second. To monitor inward and outward currents over time, we analyzed the current size at -80 and + 80 mV of the ramps. Figure 3A shows a representative trace of the current at - 80 mV over time. Both at a holding potential of -40 mV or at +70 mV, the currents are significantly larger than in cells transfected with only the GFP containing vector (Fig.: 3E). Interestingly, after changing to a positive holding potential, current size in Trp8 transfected cells slowly increases and reaches steady state after approximately 70 seconds (Fig.: 3A). To determine the selectivity of the induced currents, we then perfused the cells with solutions that either contain no sodium, no added Ca2+ (Fig. 3A, C) or a sodium containing, but divalent ion free bath solution. To control for the effect of the solution change alone, we also perfused with normal bath (see puff in Fig. 3A). While removal of external Ca²⁺ completely abolishes the trp 8 induced currents - the remaining current being identical in size and shape to the control (Fig.: 3A, C, E), removal of external sodium has no effect (Fig.: 3E). An important hallmark of calcium selective channels (e.g. Vennekens, R., Hoenderop, G.J., Prenen, J., Stuiover, M., Willems, PHGM, Droogmans, G., Nilius, B.and Bindels, R.J.M (1999) J. Biol. Chem. 275, 3963-3969), is their ability to conduct sodium only if all external divalent ions, namely Ca²⁺ and magnesium are removed. To test whether the trp 8 channel conforms with this phenomenon normal bath solution was switched to a solution containing only sodium and 1 mM EGTA. As can be seen in Figure 3B and D, Trp8 transfected cells can now conduct very large sodium currents. Interestingly, immediately after the solution change, the currents first become smaller before increasing rapidly, indicating that the pore may initially still be blocked by calcium a phenomenon usually called anomalous mole fraction behaviour (Warnat, J., Philipp, S., Zimmer, S., Flockerzi, V., and Cavalié A.(1999) J.Physiol. (Lond) 518, 631-638). The measured outward currents of Trp8 transfected cells in normal bath solution are not significantly different from non-transfected control cells or cells which only express the reporter gene GFP. As the removal of external Ca2+ abolishes the Trp8 specific current, the remaining current was subtracted from the current before the solution change to obtain the uncontaminated Trp8 conductance (see inset in Fig.: 3C). As expected from the given ionic conditions (high EGTA inside, 2 mM Ca2+ outside), the current-voltage relationship now shows prominent inward rectification with little to no outward current.

Both the time course of the development of Trp8 currents and the size of the currents depend on the frequency of stimulation (data not shown), the internal and external Ca²⁺ concentration

and the resting membrane potential, suggesting that Trp8 calcium conductance is intrically regulated by a Ca²⁺ mediated feedback mechanisms.

Example 6: Ca2+/calmodulin binds to the C-terminus of the Trp8 protein

To test whether calmodulin, a prime mediator of calcium regulated feedback, is involved, first it was investigated biochemically whether Trp8 protein can bind calmodulin. Trp8 cDNA was in vitro translated in the presence of ³⁵S-methionine and the product incubated with calmodulin-agarose beads. After several washes either in the presence or abscence of Ca²⁺, the beads were incubated in Laemmli buffer and subjected to SDS-polyacrylamide gel electrophoresis. In the presence of Ca²⁺ (1mM), but not in the absence of Ca²⁺, Trp8 protein binds to calmodulin (Fig.: 4B).

To narrow down the binding site, two approaches were undertaken: Firstly, GST-TRP8 fusion proteins of various intracellular domains of Trp8 were constructed, expressed in E. coli and bound to gluthathione sepharose beads. These beads were then incubated with in vitro translated 35S- labeled calmodulin, washed and subjected to gel electrophoresis. Secondly, truncated versions of in vitro translated Trp8 protein were used in the above described binding to calmodulin-agarose. As shown in Figure 4A, and C, fusion proteins of the N-terminal region (N1, N2) of Trp8 did not bind calmodulin, while C-terminal fragments (C1, C2, C3, C4) showed calmodulin binding in the presence of calcium (for localization of fragments within the entire Trp8 protein see Fig. 4C). Accordingly, a truncated version of in vitro translated Trp8, which lacks the C-terminal 32 amino acid residues did not bind to calmodulin-agarose (4B). We have restricted the calmodulin binding site to amino acid residues 691 to 711 of the Trp8 protein. This calmodulin binding site does not resemble the typical conserved IQ - motif of conventional myosins, but has limited sequence homology to the calcium dependent calmodulin binding site 1 of the transient receptor potential like (trpl) protein of Drosophila melanogaster (Warr and Kelly, 1996) with several charged amino acid residues conserved. The sequence of the calmodulin binding site of the Trp8 protein resembles a putative amphipathic α-helical wheel structure with a charged and a hydrophobic site according to a model proposed by Erickson-Vitanen and De Grado (1987, Methods Enzymol. 139, 455-478.).

Example 7: Expression of Trp8 transcripts in human placenta and pancreas

Several slides from a human placenta of a ten week old abort were used for in situ hybridization experiments. The in situ hybridization experiments revealed expression of Trp8 transcripts in human placenta (Fig.: 5B). Expression was detectable in trophoblasts and syncytiotrophoblasts of the placenta, but not in Langhans cells.

Trp8 transcripts are detectable in human pancreas (Fig.: 5A). Therefore Trp8 probes were hybridized to tissue sections of human pancreas. The pancreatic tissues were removed from patients with pancreas cancer. Trp8 expression is detectable in pancreatic acinar cells, but not in Langerhans islets (Fig.: 5C). No Trp8 expression was found in regions of pancreatic carcinomas (data not shown).

Furthermore, the Trp8 cDNA is not detectable in human colon nor in human kidney by in situ hybridization as well as by Northern analysis (Fig.: 5A, D). The Northern results taken together with the in situ expression data indicate that the Trp8 protein is not the human ortholog of the CaT1 and ECaC channels cloned from rat intestine (Peng, J.B., Chen, X.Z., Berger, U.V., Vassilev, P.M., Tsukaguchi, H., Brown, E.M. and Hediger M.A.(1999) J Biol Chem. 6;274, 22739-22746) and from rabbit kidney (Hoenderop, J.G., van der Kemp, A.W., Hartog, A., van de Graaf, S.F., van Os, C.H., Willems, P.H. and Bindels, R.J. (1999) J Biol Chem. 26;274, 8375-8378), respectively. Trp8 is unlikely to represent the human version of CaT1 as its expression is undetectable in the small intestine and colon tissues where CaT1 is abundantly expressed. If, however, Trp8 is the human version of rat CaT1, a second gene product appears to be required for Ca²⁺ uptake in human small intestine and colon attributed to CaT1 in rat small intestine and colon.

Example 8: Differential expression of Trp8 transcripts in benign and malign tissue of the prostate

The Trp8 transcripts are expressed in human prostate as shown by hybridization of a Trp8 probe to a commercial Northern blot (Clontech, Palo Alto, USA) (Fig.: 5A). Trp8 transcripts were not detectable by Northern blot analysis using pooled mRNA of patients with benign prostatic hyperplasia (BPH) (Fig.: 5A, prostate*). To examine Trp8 expression on the cellular

level, sections of prostate tissues were hybridized using Trp8 specific cDNA probes (Table 3). Expression of Trp8 transcripts is not detectable in normal prostate (n = 3), benign hyperplasia (BPH, n = 15) or prostatic intraepithelial neoplasia (PIN, n = 9) (Fig.: 6A, C, E). Trp8 transcripts were only detectable in prostate carcinoma (PCA), although with different expression levels. Low expression levels were found in primary carcinomas (2 - 10 % of the carcinoma cells, n = 8) (Fig.: 7B). Much stronger expression was detectable in rezidive carcinoma (10 - 60 %) (Fig.: 7D, n = 6) and metastases of the prostate (60 - 90 %, n = 4) (Fig.: 7F). Thus it has to be concluded that the commercial Northern blot used in Fig.: 5A contains not only normal prostate mRNA as indicated by the distributor. According to the distributors instructions the prostate mRNA used for this Northern blot was collected from 15 human subjects in the range of 14 to 60 years of age. This prostate tissue was not examined by pathologic means. Since Trp8 expression is not detectable in normal or benign prostate, this finding implicates that the mRNA used for this Northern blot was extracted in part from prostatic carcinoma tissue. To summarize, Trp8 expression is only detectable in malign prostate and, thus, the Trp8 cDNA is a marker for prostate carcinoma. The results are summarized in Table 4.

Table 3

Trp8 probes used for in situ hybridization:

Probes (antisense)

- 1.) 5' TCCGCTGCCGGTTGAGATCTTGCC 3'
- 2.) 5' CTTGCTCCATAGGCAGAGAATTAG 3'
- 3.) 5' ATCCTCAGAGCCCCGGGTGTGGAA3'

Controls (sense)

- 1.) 5' GGCAAGATCTCAACCGGCAGCGGA 3'
- 2.) 5' CTAATTCTCTGCCTATGGAGCAAG 3'
- 3.) 5' TTCCACACCCGGGGCTCTGAGGAT 3'

Table 4

Prostate	total	negative	positive
normal	3	3	0
ВРН	15	15	0
PIN	9	9	0

carcinoma 18 1 17

(B) Differential expression of Trp8 transcripts in benign and malign tissue of the uterus

Moreover it could be shown that Trp8 is expressed in endometrial cancer (also called cancer of the uterus, to be distinguished from uterine sarcoma or cancer of the cervix) whereas no expression was observed in normal uterus tissue. Thus, Trp8 also is a specific marker for the diagnosis of the above cancer (Fig. 12).

Example 9: Characterization of Trp9

The complete protein coding sequence of Trp9 was determined (Fig. 9). Trp 9 transcripts are predominantly expressed in the human prostate and in human colon. As it could be shown by Northern blot analysis, there is no difference of the expression of TRP9 in benigne prostata hyperplasia (BPH, Fig. 13, upper panel left) or prostate carcinoma (Fig. 13, upper panel right). However, Trp9 is useful as a reference marker for prostata carcinoma, i.e. can be used for quantifying the expression level of Trp8. The ratio of the expression of Trp8:Trp9 in patients and healthy individuals is useful for the development of a quantitative assay.

Example 10: Characterization of Trp10

The complete protein coding sequence of TRP10 (a and b) was determined by biocomputing (Fig. 10 and 11). Using a 235 bp fragment of the Trp10 cDNA as probe in Northern blot analysis TRP10 transcripts could only be detected in mRNA isolated from individuals with prostate cancer (Fig. 13, bottom panel) but not in mRNA isolated from benign tissue of the prostate (prostate BPH) nor in mRNA isolated from heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. The 235 bp cDNA fragment of the Trp10 cDNA was amplified using the primer pair UW248 5'-ACA GCT GCT GGT CTA TTC C-3' and UW249 5'-TAT

GTG CCT TGG TTT GTA CC-3' and prostate cDNA as template. In summary, Trp10a and Trp10b, like TRP8 are also expressed in malignant prostate tissue. So far, its expression could not be observed in any other tissue examined (see above). Thus, Trp 10a and Trp10b are also useful markers which are specific for malignant prostate tissue.

Furthermore, database searches in public databases of the national center for biological information (NCBI) revealed the existence of several expressed sequence tags (EST clones) being in part identical to the Trp10 sequence. These EST clones were originally isolated from cancer tissues of lung, placenta, prostate and from melanoma. These clones include the clones with the following accession numbers: BE274448, BE408880, BE207083, BE791173, AI671853, BE390627. The results demonstrate that cancer cells of these tissues express Trp10 related transcripts whereas no expression of Trp10 transcripts in the corresponding healthy tissues are detectable (Figure 13). Furthermore, it could be shown that in cancer cells of melanoma and prostate cancer Trp10 transcripts are expressed as shown by in situ hybridizations using 4 antisense probes (Figure 14A – E and 13K-O and Table 2, above). Furthermore, it could clearly be shown that cancer cells of these tissues expressing Trp10 transcripts also express Trp10-antisense transcripts as shown in Figure 14F-J, Figure 14P-R and Figure 14T by in situ hybridizations using 4 sense probes (Table 2, above). The in situ hybridization experiments demonstrate that detection of a subset of cancer cells derived from carcinoma of lung, placenta, prostate and melanoma is feasible using antisense as well as sense probes complementary to Trp10 transcripts or complementary to Trp10-antisense transcripts, respectively.

The foregoing is meant to illustrate but not to limit the scope of the invention. The person skilled in the art can readily envision and produce further embodiment, based on the above teachings, without undue experimentation.

What Is claimed Is:

1. An isolated nucleic acid molecule encoding the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b or a protein exhibiting biological properties of Trp8a, Trp8b, Trp9, Trp10a or Trp10b and being selected from the group consisting of

- (a) a nucleic acid molecule encoding a protein that comprises the amino acid sequence depicted in Figure 7, 8A, 9, 10 or 11;
- (b) a nucleic acid molecule comprising the nucleotide sequence depicted in Figure 7, 8A, 9, 10 or 11;
- (c) a nucleic acid molecule included in DSMZ Deposit No. DSM 13579, DSM 13580, DSM 13584, DSM 13581 or DSM....;
- (d) a nucleic acid molecule which hybridizes to a nucleic acid molecule specified in (a) to (c);
- (e) a nucleic acid molecule the nucleic acid sequence of which deviates from the nucleic sequences specified in (a) to (d) due to the degeneration of the genetic code; and
- (f) a nucleic acid molecule, which represents a fragment, derivative or allelic variation of a nucleic acid sequence specified in (a) to (e).
- 2. A recombinant vector containing the nucleic acid molecule of claim 1
- 3. The recombinant vector of claim 2 wherein the nucleic acid molecule is operatively linked to regulatory elements allowing transcription and synthesis of a translatable RNA in prokaryotic and/or eukaryotic host cells.
- 4. A recombinant host cell which contains the recombinant vector of claim 3.
- 5. The recombinant host cell of claim 4, which is a mammalian cell, a bacterial cell, an insect cell or a yeast cell.
- 6. An isolated protein exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b which is encoded by a nucleic acid molecule of claim 1.
- 7. A recombinant host cell that expresses the isolated protein of claim 6.

8. A method of making an isolated protein exhibiting biological properties of the human prostate carcinoma associated protein Trp8a, Trp8b, Trp9, Trp10a or Trp10b comprising: (a) culturing the recombinant host cell of claim 6 under conditions such that said protein is expressed; and

- (b) recovering said protein.
- 9. The protein produced by the method of claim 8.
- 10. An antisense RNA sequence characterized in that it is complementary to an mRNA transcribed from a nucleic acid molecule of claim 1 or a part thereof and can selectively bind to said mRNA or part thereof, said sequence being capable of inhibiting the synthesis of the protein encoded by said nucleic acid molecule.
- 11. A ribozyme characterized in that it is complementary to an mRNA transcribed from a nucleic acid molecule of claim 1 or a part thereof and can selectively bind to and cleave said mRNA or part thereof, thus inhibiting the synthesis of the protein encoded by said nucleic acid molecule.
- 12. An inhibitor characterized in that it can suppress the activity of the protein of claim 6.
- 13. A method for diagnosing a prostate carcinoma which comprises contacting a target sample suspected to contain the protein Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA with a reagent which reacts with Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA and detecting Trp8a, Trp8b, Trp10a and/or Trp10b or the Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA.
- 14. The method of claim 13, wherein the reagent is a nucleic acid.
- 15. The method of claim 13, wherein the reagent is an antibody.
- 16. The method of claim 13, wherein the reagent is detectably labeled.

17. The method of claim 16, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

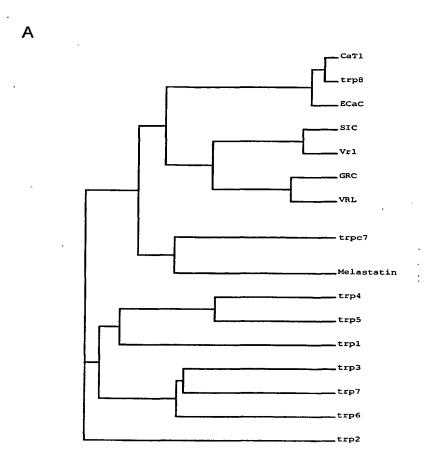
- 18. A method for diagnosing an endometrial cancer (carcinoma of the uterus) which comprises contacting a target sample suspected to contain the protein Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA with a reagent which reacts with Trp8a and/or Trp8b or the Trp8a and/or Trp8a and/or trp8b encoding mRNA and detecting Trp8a and/or Trp8b or the Trp8a and/or Trp8b encoding mRNA.
- 19. The method of claim 18, wherein the reagent is a nucleic acid.
- 20. The method of claim 18, wherein the reagent is an antibody.
- 21. The method of claim 18, wherein the reagent is detectably labeled.
- 22. The method of claim 21, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.
- 23. A method for diagnosing a melanoma, chorion carcinoma, cancer of the lung and of the prostate in a tissue of a subject, comprising contacting a sample with a reagent which detects Trp10a and/or Trp10b antisense RNA or Trp10a and/or Trp10b related antisense RNA.
- 24. A method for preventing, treating, or ameliorating a prostate tumor, endometrial cancer (carcinoma of the uterus) tumor, a chorion carcinoma, cancer of the lung or melanoma, which comprises administering to a mammalian subject a therapeutically effective amount of a reagent which decreases or inhibits expression of Trp8a, Trp8b, Trp10a and/or Trp10b and/or the activity of Trp8a, Trp8b, Trp10a and/or Trp10b.
- 25. The method of claim 24, wherein the reagent is a nucleotide sequence comprising an antisense RNA.

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26. The method of claim 24, wherein the reagent is a nucleotide sequence comprising a ribozyme.

- 27. The method of claim 24, wherein the reagent is an inhibitor of Trp8a, Trp8b, Trp10a and/or Trp10b.
- 28. The method of claim 27, wherein the reagent is an anti-Trp8a-, anti Trp8b-, anti-Trp10a-and/or anti-Trp10b antibody or a fragment thereof.
- 29. A diagnostic kit useful for the detection of Trp8a, Trp8b, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts in a sample, wherein the presence of an increased concentration of Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b or Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts is indicative for a prostate tumor, endometrial cancer (cancer of the uterus) tumor, a chorion carcinoma, cancer of the lung or melanoma, said kit comprising a probe for detection of Trp8a, Trp8b, Trp9, Trp10a or Trp10b or Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b encoding mRNA or Trp10a and/or Trp10b antisense transcripts.
- 30. The kit of claim 29, wherein the target component to be detected is Trp8a, Trp8b, Trp9, Trp10a and/or Trp10b and the probe is an antibody.
- 31. A method for identifying a compound which acts as an agonist or antagonist on the ion channels Trp8, Trp9 and/or Trp10, said method comprising contacting a test compound with the ion channel Trp8, Trp9 and/or Trp10, and determining whether said test compound affects the calcium uptake.

Figs. 1A and 1B



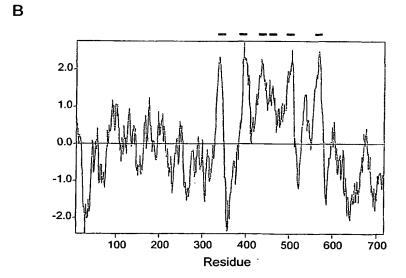
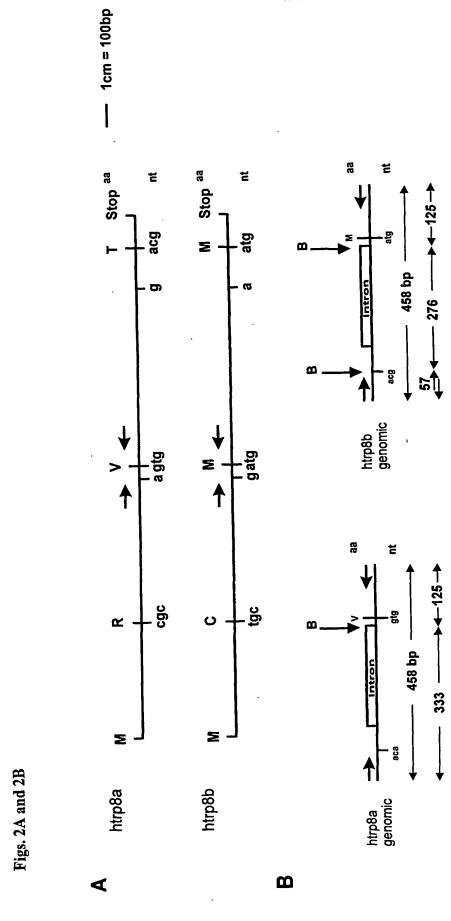


Fig. 1C

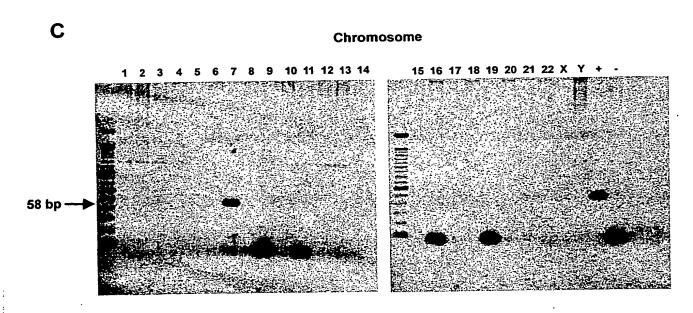
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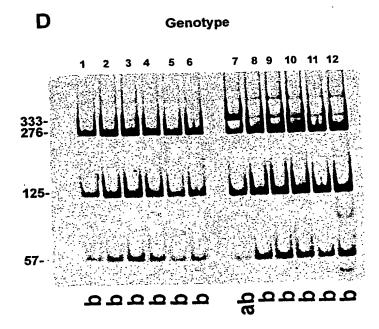
htrp8A htrp8B Vr1 ECaC	MG MG MEQRASLDSEESESPPQENSCLDPPDRDPNCKPPPVKPHIFTTRSR7RLFGKGDSEEASP MG MG	2 2 60 2
htrp8A htrp8B Vr1 ECaC	LSLÄKEKGLIICIMSKFCRWFORRESWAQSRÖEQNILQQK-ÄIWESP-IJIĀ ISLFKEKGLIICIMSKFCRWFORRESWAQSRÖEQNILQQK-ÄIWESP-IJIĀ ILCEYEEĞGIASCPITYSSVLTIQBFGCPASVPPSSQÖSVAGEKPPRIVDRRSIFDÄ ACPĒKAKGPWAQLQKILISWPVGEQDWEQYRÖRVNMLQQE-ÄIRDSP-ILQÄ	52 52 120 52
htrp8A htrp8B Vr1 ECaC	AKONDVOAĽNIKĽKYEDCKVHORGANŠEŽAŬHIKAĽ-YDN-LEAAMVÍMEAĀ AKONDVOAĽNIKĽKYEDCKVHORGANŠEŽAŬHIKAŬ-YDN-LEAAMVÍMEAĀ VAQSKOCEŽESLÍPELORSKKRITOBEEKOPETŘEČEĽKAŇINIKGONDTIALÍLUVA AKENDLRIĽKIĽLINOSCDFOORGANŠEŽAŇHVÍMAŠ-YTŇ-LEAATIĽMEAĎ	102 102 180 102
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htrp8A htrp8B Vr1 ECaC	-nvlikaehetelyvonseejanyteheydivyodricalalititob nvlikeeretelyvonseejanyteheydivyodricalalititob nvlikeeretelyvonseejantiteheydivyodricalalititob	207 207 300 207
htrp8A htrp8B Vr1 ECaC	nktéacchynllsydrhodhlopidluphhogltergagueghtumfohlug nkteacchynllisydrhodhlopidluphhogltergagueghtuhfohlug nkrytsynliiligrahethigeetthkogltergalvarsgkkoglaytigrethep nkteacchynliisydehsdhlosieluphhoglterkagueghtumpohlug	261 261 360 261
htrp8A htrp8B Vr1 ECaC	KRRHTORTYGRLTBTLYDETEYDSSGDEOBLYBLITTK-KREAR-OLEDOTFYK KRYHTORTYGBLTBTLYDETEYDSSGDEOBLYBLITTK-KREAR-OLEDOTFYK ECRHLSRYTTRAYGGYHSLYDLSCIYDC-ENGYLBVLYSSSETPRYHDHLIVEFUK KRYHVORTCOPLTBTLYDLTBYDSWGEELBTRBLVYSSK-KREAR-OLYDOTFYK	314 314 420 314
htrp8A htrp8B Vr1 ECaC	ežvslänkrygrpyřchlgaiřílý licethcciřřělkprtnurtsřrdntllogillo elvslänkrygrpyřchlgaiříly iřcethcciřřelkprtnurtsřrdntllogillo růlogickykrifytnyfvíciými iřtaravýřepeg	374 374 468 374
htrp8A htrp8B Vr1 ECaC	EAY TPRÖDIRLYGELVTVIGALIILLVEVPDIFRMGVTRFFGGTILGGPFHVLIITYAF EAY TPRÖDIRLYGELVTVIGALIILLVEVPDIFRMGVTRFFGGTILGGPFHVLIITYAFTVGDYFHVTGEILSYSGGVYFFFRGIGYFLGRFS-LKSLFVDSYSELLFFVGSL EAYVHODNIBLYGELVTTTGAVIILLLEIPDIFRVGASRYFGGTILGGPFHVIITYAS S2 S3	434 434 522 434
htrp8A htrp8B Vr1 ECaC	MYĽVIMÁMILISASCEŸVPNSĒAŠVLĒŠICNVM FARGFOMLĒPFTIMĪOKAĪFGIMARĪC MYĽVIMÁMILISASCEŸVPNSĒAŠVLĒŠICNMĀ FARGFOMLĒPFTIMĪOKAĪ FGIDMRĒC PAĽVSVYLVFSORICIĀNASHVĒSĪAMOŅTIMIJYTIRGĒOCMĢIVAVAIĒKAILADĪGRĪM LVĪLIMĀMILIMANGEŸVPLSĒAĻVLĒŠUSVĀ FARGFOMLĒPFTIMĪOKAĪ FGIDMRĒC 54	494 494 582 494
htrp8A htrp8B Vr1 ECaC	WIMAVILIĞEASAFYII FOTED	538 538 642 538
htrp8A htrp8B Vr1 ECaC	LTI I İŞPANYNVÖLPEMYSİTYARFAİ I ATLIMÜNLLIRMİĞ DİHMRVAHİR DELİRAĞI I LTI I İŞFANYNVÖLPEMYSİTTARFAİ I ATLIMÜNLLIR MƏĞ DİHMRVAHİR DELİRAĞI I GAĞDLEFTENYI İFRAVFI ÇILLAYVILIYYI İLIMMLI ALMƏĞ DİVNKI İŞÇESINLIK ÇÖR LTI I İŞFANYSVÖLPEMYÇİTYAR FAZI I ATLIMINLETIM MEĞ DİHMRVİ ÖĞRDELİRAĞIV S6	598 598 702 598
htrp8A htrp8B Vr1 ECaC	VATTVMLERKLPRCLMP-RSGICGREYGLGD-RWFLRVEDRODLMRORIORYAQA VATTVMLERKLPRCLMP-RSGICGREYGLGD-RWFLRVEDRODLMRORIORYAQA AITILDTEKSFLKCMRKAFRSGKLLQYGFTPDGKODYANCFRVDEVMYTTMNTNVGIINE VATTVMLERKMPRFLMP-RSGICGYEYGLGD-RWFLRYENHHDONPLRVLRYVEA	671 671 762 671
htrp8A htrp8B Vr1 ECaC	fhträsedlokdsv-eklelöcpfsphislphesvsrstsrssanwerlrostlrr fhträsedlokdsv-eklelöcpfsphislphesvsrstsrssanwerlrostlrr dpgw-cegvkrtlsfslesgrvärnnknfrlvphlirdsstrdrhatogesvolkhto fkcsdkedgoeolsekrp-stvesghisrasvafotpslsrttsossn—skrgweilrr	726 72 <i>6</i> 820 728
htrp8A htrp8B Vr1 ECaC	DLRGI INRGLEDGESWEYQI * DLRGI INRGLEDGESWEYQI * SLKPEDAEVFKDSMVFGEK* NTLGHLNLGLDLGEGDGEEVYHF*	746 746 839 751



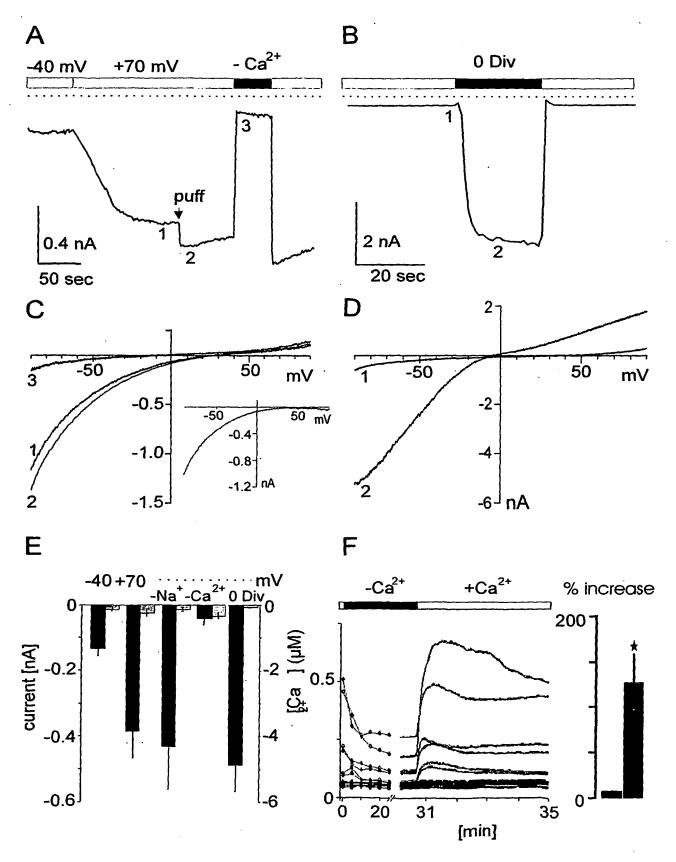
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Figs. 2C and 2D

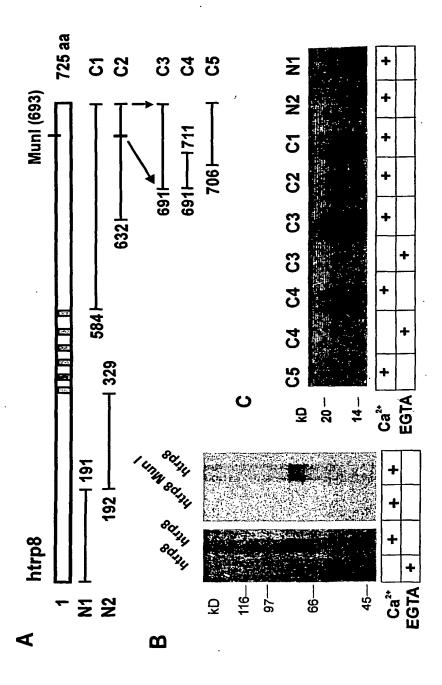




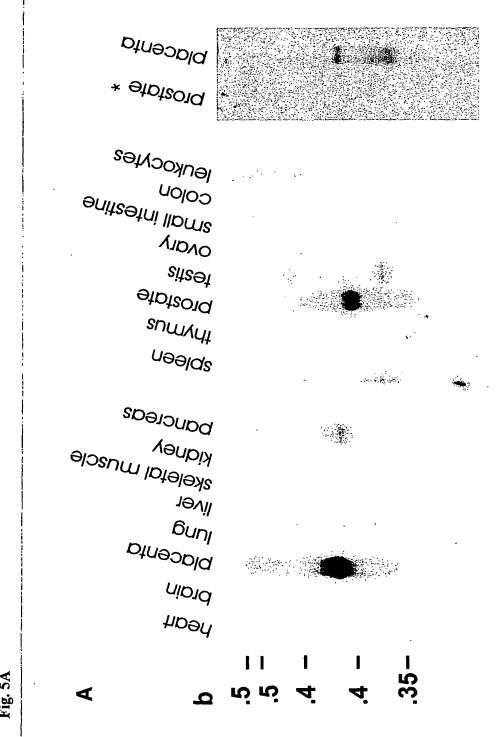
Figs. 3A - 3F



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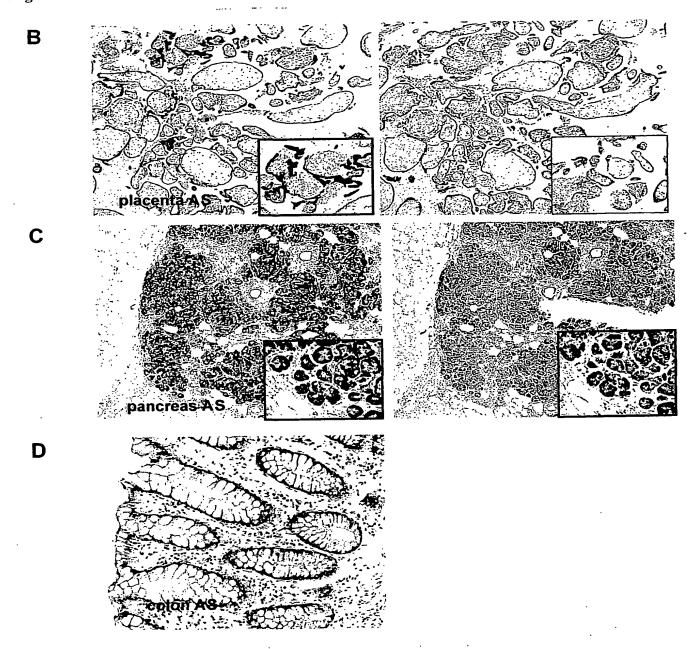


Figs. 4A - 4C

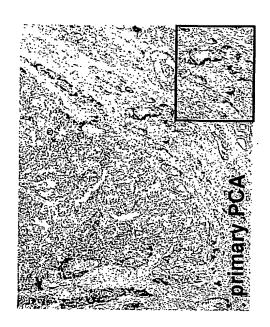


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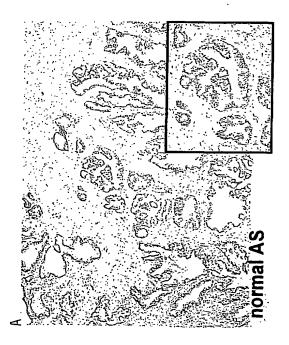
Figs. 5B - 5D

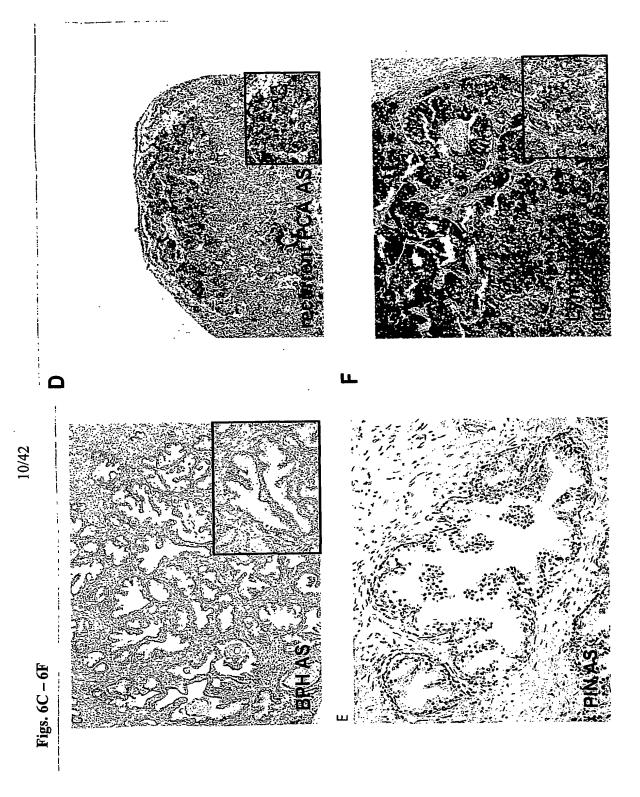


Figs. 6A and 6B



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Fig. 7 / continuation 2

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2650	2670	2690
TCACCCTTCCGACAGGAG	CACTGCATGTCAGAGCACTT	TAAAAACAGGCCAGCCTGCTTG
2710	2730	2750
GGCCCTCGGTCTCCACCC	CAGGGTCATAAGTGGGGAGA	GAGCCCTTCCCAGGGCACCCAG
2770	2790	2810
GCAGGTGCAGGGAAGTGC	AGAGCTTGTGGAAAGCGTGT	GAGTGAGGGAGACAGGAACGGC
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MGLSLPKEKGLILCLWSKFCRWFQRRESWAQSRDEQNLLQQKRIWESPLLLAAKDNDVQALNKLLKYEDCKVHQRGAMGETALHIA ALYDNLEAAMVLMEAAPELVFEPMTSELYEGQTALHIAVVNQNMNLVRALLARRASVSARATGTAFRRSPRNLIYFGEHPLSFAAC VNSEEIVRLLIEHGADIRAQDSLGNTVLHILILQPNKTFACQMYNLLLSYDRHGDHLQPLDLVPNHQGLTPFKLAGVEGNTVMFQH LMQKRKHTQWTYGPLTSTLYDLTEIDSSGDEQSLLELIITTKKREARQILDQTPVKELVSLKWKRYGRPYFCMLGAIYLLYIICFT MCCIYRPLKPRTNNRTSPRDNTLLQQKLLQEAYVTPKDDIRLVGELVTVIGAIIILLVEVPDIFRMGVTRFFGQTILGGPFHVLII TYAFMVLVTMVMRLISASGEVVPMSFALVLGWCNVMYFARGFQMLGPFTIMIQKMIFGDLMRFCWLMAVVILGFASAFYIIFQTED PEELGHFYDYPMALFSTFELFLTIIDGPANYNVDLPFMYSITYAAFAIIATLLMLNLLIAMMGDTHWRVAHERDELWRAQIVATTV MLERKLPRCLWPRSGICGREYGLGDRWFLRVEDRQDLNRQRIQRYAQAFHTRGSEDLDKDSVEKLELGCPFSPHLSLPTPSVSRST SRSSANWERLRQGTLRRDLRGIINRGLEDGESWEYQI

Figure 8:

ATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCT MGLSLPKEKGLILC 290 270 GCCTATGGAGCAAGTTCTGCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAG L W S K F C R W F Q R R E S W A Q S R D 330 350 ATGAGCAGAACCTGCTGCAGCAGAAGAGGATCTGGGAGTCTCCTTCTTAGCTGCCA EQNLLQQKRIWESPLLLAAK 410 390 370 AAGATAATGATGTCCAGGCCCTGAACAAGTTGCTCAAGTATGAGGATTGCAAGGTGCACC D N D V Q A L N K L L K Y E D C K V H Q 470 450 AGAGAGGAGCCATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGG RGAMGETALHIAALYDNLEA 530 510 CCGCCATGGTGCTGATGGAGGCTGCCCCGGAGCTGGTCTTTGAGCCCCATGACATCTGAGC A M V L M E A A P E L V F E P M T S E L 590 570 TCTATGAGGGTCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGC Y E G Q T A L H I A V V N Q N M N L V R 650 630 GAGCCCTGCTTGCCCGCAGGGCCAGTGTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCC A L L A R R A S V S A R A T G T A F R R 710 690 670 GTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGCCTGTGTGA S P C N L I Y F G E H P L S F A A C V N Fig. 8 / continua in 1

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TCA M TCC L

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Fig. 8 / continu: on 2

IAMMGDTHWRVAHERDELWR 2030 2010 1990 GGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGTGGC A Q I V A T T V M L E R K L P R C L W P 2090 2050 2070 CTCGCTCCGGGATCTGCGGACGGGAGTATGGCCTGGGAGACCGCTGGTTCCTGCGGGTGG RSGICGREYGLGDRWFLRVE 2150 2130 2110 AAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCTTCCACACCC RQDLNRQRIQRYAQAFHTR 2190 2170 GGGGCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCA GSEDLDKDSVEKLELGCPFS 2270 2250 GCCCCACCTGTCCCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCA P H L S L P M P S V S R S T S R S S A N 2330 2310 ATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGAGACCTGCGTGGGATAATCAACAGGG W E R L R Q G T L R R D L R G I I N R G 2370 2390 GTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGA LEDGESWEYQI *

MGLSLPKEKGLILCLWSKFCRWFQRRESWAQSRDEQNLLQQKRIWESPLLLAAKDNDVQALNKLLKYEDCKVHQRGAMGETALHIA ALYDNLEAAMVLMEAAPELVFEPMTSELYEGQTALHIAVVNQNMNLVRALLARRASVSARATGTAFRSPCNLIYFGEHPLSFAAC VNSEEIVRLLIEHGADIRAQDSLGNTVLHILILQPNKTFACQMYNLLLSYDRHGDHLQPLDLVPNHQGLTPFKLAGVEGNTVMFQH LMQKRKHTQWTYGPLTSTLYDLTEIDSSGDEQSLLELIITTKKREARQILDQTPVKELVSLKWKRYGRPYFCMLGAIYLLYIICFT MCCIYRPLKPRTNNRTSPRDNTLLQQKLLQEAYMTPKDDIRLVGELVTVIGAIIILLVEVPDIFRMGVTRFFGQTILGGPFHVLII TYAFMVLVTMVMRLISASGEVVPMSFALVLGWCNVMYFARGFQMLGPFTIMIQKMIFGDLMRFCWLMAVVILGFASAFYIIFQTED PEELGHFYDYPMALFSTFELFLTIIDGPANYNVDLPFMYSITYAAFAIIATLLMLNLLIAMMGDTHWRVAHERDELWRAQIVATTV MLERKLPRCLWPRSGICGREYGLGDRWFLRVEDRQDLNRQRIQRYAQAFHTRGSEDLDKDSVEKLELGCPFSPHLSLPMPSVSRST SRSSANWERLRQGTLRRDLRGIINRGLEDGESWEYQI

B)

 $\verb|CCTCTACAGGGAGACGGTGGGCCCCTTGGGGGGGGCTGATGTGGCCCCAAGGCTGAGTCCCGTCAGGGTCTGGCCTCAGGCCTCAGGGCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGAGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGGCCTCAGGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGCTCAGGGTCTGAGGCTCAGGGTCTGAGGTCTGAGGTCTGAGGTCTCAGGGTCTGAGGTCTCAGGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGTCTGAGGT$ GGCCCCCAAGGAGCCGGCCCTACACCCCATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCTGCCTATGGAGCAAGTTCT GCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAGATGAGCAGAACCTGCTGCAGCAGAAGAGAGATCTGGGAGTCTCCT CATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGGCCGCCATGGTGCTGATGGAGGCTGCCCCGGAGCTGG TCTTTGAGCCCATGACATCTGAGCTCTATGAGGGTCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGA GCCCTGCTTGCCCGCAGGGCCAGTGTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCCGTAGTCCCCGCAACCTCATCTACTTTGG GGAGCACCCTTTGTCCTTTGCTGCCTGTGTGAACAGTGAGGAGCTCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCGGGCCC TGCAGAAGCGGAAGCACCCAGTGGACGTATGGACCACTGACCTCGACTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGAT GAGCAGTCCCTGCTGGAACTTATCATCACCACCAAGAAGCGGGAGGCTCGCCAGATCCTGGACCAGACGCCGGTGAAGGAGCTGGT GAGCCTCAAGTGGAAGCGGTACGGGCGGCCGTACTTCTGCATGCTGGGTGCCATATATCTGCTGTACATCATCTGCTTCACCATGT GCTGCATCTACCGCCCCTCAAGCCCAGGACCAATAACCGCACAAGCCCCCGGGACAACACCCTCTTACAGCAGAAGCTACTTCAG GAAGCCTACGTGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCTGGTGACTGTCATTGGGGCTATCATCCTGCTGGTAGA GGTTCCAGACATCTTCAGAATGGGGGTCACTCGCTTCTTTGGACAGACCATCCTTGGGGGCCCATTCCATGTCCTCATCATCACCT GCCCTGTTCAGCACCTTCGAGCTGGTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCAT CCCATGAGCGGGATGAGCTGTGGAGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGTGGCCT CGCTCCGGCATCTGCGGACGGGAGTATGGCCTGGGGGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCG c.)

CAAACTCACAGCCCTCTCCAAACTGGCTGGGGCTGCTGGGAGACTCCCAAGGAACTCGTCAGGAAGGCAGGAGACACGAGACACGGA  ${\tt CCTCTACASEGAGACGGTGGGCCGTTGGGGGGGGTGATGTGGCCCCAAGGCTGAGTCCCGTCAGGGTCTGGCCTCAGGCCTCAGGGTCAGGGTCTGGCCCTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGGTCAGGTCAGGTCAGGTCAGGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCAGGTCA$ GGCCCCCAAGGAGCCGGCCCTACACCCCATGGGTTTGTCACTGCCCAAGGAGAAAGGGCTAATTCTCTGGCCTATGGAGCAAGTTCT GCAGATGGTTCCAGAGACGGGAGTCCTGGGCCCAGAGCCGAGATGAGCAGAACCTGCTGCAGCAGAAGAGGATCTGGGAGTCTCCT CTCCTTCTAGCTGCCAAAGATAATGATGTCCAGGCCCTGAACAAGTTGCTCAAGTATGAGGATTGCAAGGTGCACCAGAGAGGAGGAGC TCTTTGAGCCCATGACATCTGAGCTCTATGAGGTCCTGACTGCCCATCACTTGAACGCCTGCCCCTGAAATGCCAGGGCCTAGAG AAGAGGAAGAGATGGGCAGCTGGATCCCCTGGGAATCCTGAACACCCGAGAGCTCCCTGTTCTCCATCCCAGGCTACCCCTGA TCAGACTGCACTCCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGAGCCCTGCTTGCCCGCAGGGCCCAGTGTCTCTGCCA GAGCCACAGGCACTGCCTTCCGCCGTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGCCTGTGTGAAC AGATGTACAACCTGTTGCTGTCCTACGACAGACATGGGGACCACCTGCAGCCCCTGGACCTCGTGCCCCAATCACCAGGGTCTCACC CCTTTCAAGCTGGCTGGAGTGCAGGGTAACACTGTGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACACCCAGTGGACGTATGG ACCACTGACCTCGACTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGATGAGCAGTCCCTGGGAACTTATCATCACCACCA AGAAGCGGGAGGCTCGCCAGATCCTGGACCAGACGCCGGTGAAGGAGCTGGTGAGCCTCAAGTGGAAGCGGTACGGGCGGCCGTAC TTCTGCATGCTGGGTGCCATATATCTGCTGTACATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAA TAACCGCACGAGCCCCCGGGACACACCCTCTTACAGCAGAAGCTACTTCAGGAAGCCTACATGACCCCTAAGGACGATATCCGGC TGGTCGGGGGGCTGCTGTCATTGGGGCTATCATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAATGGGGGTCACTCGC TTCTTTGGACAGACCATCCTTGGGGGCCCATTCCATGTCCTCATCACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCC GCTCATCAGTGCCAGCGGGAGGTGGTACCCATGTCCTTTGCACTCGTGCTGGGCTGGTGCAACGTCATGTACTTCGCCCGAGGAT ATCCTGGGCTTTGCTTAGACAGAGGCCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCTTCGAGCT GGTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCATCACCTATGCTGCCTTTGCCATCA AGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGTGGCCTCGCTCCGGGATCTGCGGACGGGA GTATGGCCTGGGAGACCGCTGCTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCT TCCACACCCGGGGCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCAGCCCCCACCTGTCCCTT CCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGACCTGCG TGGGATAATCAACAGGGGTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCTGGAACTT GCTCTCATTTCCTGGGTGCATCAAACAAAACAAAACCAAACACCCAGAGGTCTCATCTCCCCAGGCCCCCAGGGAAAAGAGGAGT AGCATGAACGCCAAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGAAGCCCAGCC CAAGCACGGGGCTGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCATCACCCTTCCGACAGGAGCACTGCATGTCAGAGCACTT TAAAAACAGGCCAGCCTGCTTGGGCCCTCGGTCTCCACCCCAGGGTCATAAGTGGGGAGAGAGCCCTTCCCAGGGCACCCAGGCAG 

D.)

Fig. 8 / continuation 4

ATGGGGACCACCTGCAGCCCTGGACCTCGTGCCCAATCACCAGGGTCTCACCCCTTTCAAGCTGGAGTGGAGTGGAGGGTAACACT GTGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACACCCAGTGGACGTATGGACCACTGACCTCGACTCTATGACCTCACAGA GATCGACTCCTCAGGGGATGAGCAGTCCCTGGGAACTTATCATCACCACCAAGAAGCGGGAGGCTCGCCAGATCCTGGACCAGA CGCCGGTGAAGGAGCTGAGCCTCAAGTGGAAGCGGTACGGGCGCCGTACTTCTGCATGCTGGGTGCCATATATCTGCTGTAC ATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAATAACCGCACAAGCCCCCGGGACAACACCCCTCTT ACAGCAGAAGCTACTTCAGGAAGCCTACGTGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCTGGTGACTGTCATTGGGGGCTA TCATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAATGGGGGGTCACTCGCTTCTTTGGACAGACCATCCTTGGGGGCCCCATTC CATGTCCTCATCATCACCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCAGCGGGGAGGTGGTACCCAT GTCCTTTGCACTCGTGCTGGGCTGCTGCAACGTCATGTACTTCGCCCGAGGATTCCAGATGCTAGGCCCCTTCACCATCATGATTC TTCCAGACAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCTTCGAGCTGGTCCTTACCAT CATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCATCACCTATGCTGCCTTTGCCATCATCGCCACACTGC GGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCACAGGCCTTCCACACCCGGG GCTCTGAGGATTTGGACAAAGACTCAGTGGAAAAACTAGAGCTGGGCTGTCCCTTCAGCCCCCACCTGTCCCTTCCTACGCCCTCA GTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGAGACCTGCGTGGGATAATCAA CAGGGGTCTGGAGGACGGGGAGGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCTGGAACTTGCTCTCATTTTC AAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGAAGCCCAGCCCAAGCACGGGGC TEGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCATCACCCTTCCGACAGGAGCACTGCATGTCAGAGCACTTTAAAAACAGGCC GCAGAGCTTGTGGAAAGCGTGTGAGTGAGGGAGACAGGAACGGCTCTGGGGGTGGGGAAGTGGGGCTAGGTCTTGCCAACTCCATCT 

E.)

CACACATGGGGCCTCCCAGGAGTGCCCAGGACCTCGTGCTGTTGGCCTCTGAATCTATCGTCTCCAATCCGCTGTCCCACAGAAGC CATATAACCCACCTCTCTGTAAATGCCAGGAGCCATGGGGGAAACAGCGCTACACATAGCAGCCCTCTATGACAACCTGGAGGCCG CCATGGTGCTGATGGAGGCTGCCCCGGAGCTGGTCTTTGAGCCCCATGACATCTGAGCTCTATGGAGGGTGAGGGCCCCACGGGTCTG CCTACTCTTTTTSTCTTCTCTGTCTCCCTTCCGTGTCAGTCCCTGACTGCCCATCACTTGAACGCCTGCCCCCTGAAATGCCAGGG GCCTAGAGAAGAGGAAGAGATGGGCAGCAGCTGGATCCCCTGGGAATCCTGAACACCCGAGAGTCCCTGTTCTCCATCCCAGGCT  $\tt CTGGGCCAGGTCAGACTGCACTGCACATCGCTGTTGTGAACCAGAACATGAACCTGGTGCGAGCCCTGCTTGCCCGCAGGGCCAGT$ GTCTCTGCCAGAGCCACAGGCACTGCCTTCCGCCGTAGTCCCTGCAACCTCATCTACTTTGGGGAGCACCCTTTGTCCTTTGCTGC CTGTGTGAACAGTGAGGAGATCGTGCGGCTGCTCATTGAGCATGGAGCTGACATCCGGGCCCAGGACTCCCTGGATGTACAACCTG TTGCTGTCCTACGACAGACATGGGGACCACCTGCAGCCCCTGGACCTCGTGCCCAATCACCAGGGTCTCACCCCCTTTCAAGCTGGC TGGAGTGGAGGGTAACACTGTGATGTTTCAGCACCTGATGCAGAAGCGGAAGCACACCCAGTGGACGTATGGACCACTGACCTCGA CTCTCTATGACCTCACAGAGATCGACTCCTCAGGGGATGAGCAGTCCCTGCTGGAACTTATCATCACCACCAAGAAGCGGGAGGCT CGCCAGATCCTGGACCAGACGCCGGTGAAGGAGCTGGTGAGCCTCAAGTGGAAGCGGTACGGGCCGTACTTCTGCATGCTGGG TGCCATATATCTGCTGTACATCATCTGCTTCACCATGTGCTGCATCTACCGCCCCCTCAAGCCCAGGACCAATAACCGCACGAGCC CCCGGGACAACACCCTCTTACAGCAGAAGCTACTTCAGGAAGCCTACATGACCCCTAAGGACGATATCCGGCTGGTCGGGGAGCTG GTGACTGTCATTGGGGCTATCATCATCCTGCTGGTAGAGGTTCCAGACATCTTCAGAATGGGGGTCACTCGCTTCTTTGGACAGAC CATCCTTGGGGGGCCCATTCCATGTCCTCATCACCCTATGCCTTCATGGTGCTGGTGACCATGGTGATGCGGCTCATCAGTGCCA GCGGGGAGGTGGTACCCATGTCCTTTGCACTCGTGCTGGGCTGGTGCAACGTCATGTACTTCGCCCGAGGATTCCAGATGCTAGGC TTCAGCCTTCTATATCATCTTCCAGACAGAGGACCCCGAGGAGCTAGGCCACTTCTACGACTACCCCATGGCCCTGTTCAGCACCT TCGAGCTGGTCCTTACCATCATCGATGGCCCAGCCAACTACAACGTGGACCTGCCCTTCATGTACAGCATCACCTATGCTGCCTTT GCTGTGGAGGGCCCAGATTGTGGCCACCACGGTGATGCTGGAGCGGAAGCTGCCTCGCTGCCTGGCCTCGCTCCGGGATCTGCG GACGGGAGTATGGCCTGGGAGACCGCTGGTTCCTGCGGGTGGAAGACAGGCAAGATCTCAACCGGCAGCGGATCCAACGCTACGCA GTCCCTTCCTATGCCCTCAGTGTCTCGAAGTACCTCCCGCAGCAGTGCCAATTGGGAAAGGCTTCGGCAAGGGACCCTGAGGAGA ACCTGCGTGGGATAATCAACAGGGGTCTGGAGGACGGGGAGAGCTGGGAATATCAGATCTGACTGCGTGTTCTCACTTCGCTTCCT GGAACTTGCTCTCATTTTCCTGGGTGCATCAAACAAAACAAAAACCAAACACCCAGAGGTCTCATCTCCCAGGCCCCAGGGAGAAA GAGGAGTAGCATGAACGCCAAGGAATGTACGTTGAGAATCACTGCTCCAGGCCTGCATTACTCCTTCAGCTCTGGGGCAGAGGAAG CCCAGCCCAAGCACGGGGCTGGCAGGGCGTGAGGAACTCTCCTGTGGCCTGCTCATCACCCTTCCGACAGGAGCACTGCATGTCAG AGCACTTTAAAAACAGGCCAGCCTGCTTGGGCCCTCGGTCTCCACCCCAGGGTCATAAGTGGGGGAGAGAGCCCTTCCCAGGGCACCC

Fig. 8 / continuation 5

WO 02/010382 PCT/EP01/08309

Figure 9:

A.

		10							30						5	0			
CGGG	GCC	CTG	GGC	TGC	AGG	AGG	TTG	CGG	CGG	CCG	CGG	CAG	CAT	GGT	GGT	GCC	GGA	GAA	GG
													M	V	V	P	E	K	E
		70							90						11	0			
AGCA	GAG	CTG	GAT	CCC	CAA	GAT	CTT	CAA	GAA	GAA	GAC	CTG	CAC	GAC	GTT	CAT	AGT	TGA	CT
Q	S	W	Ι	P	K	I	F	K	K	K	T	С	T	T	F	I	v	D	S
	:	130						1	50						17	0			
CCAC	AGA!	rcc	GGG	AGG	GAC	CTT	GTG	CCA	GTG	TGG	GCG	ccc	CCG	GÁC	CGC	CCA	CCC	CGC	AG
T	D	P	G	G	T	L	С	Q	С	G	R	P	R	T	А	н	P	A	v
		190						.2	10						23	0			
TGGC	CAT	GA	GGA	TGC	:СТТ	CGG	GGC	AGC	CGT	GGT	GAC	CGT	GTG	GGA	CAG	CGA	TGC	ACA	CA
A	M	E	D	A	F.	G	A		v	v	т	v	W	D	s		A	Н	T
		250	_			•			70	•	-	•	••	_	29	_			_
CCAC			פרר	יראר	CCD	ጥርር	<u>'</u>	_		ር ጥ	CCA	سس	ראר	ccc		-	ברפ	ממח	ദ്ര
T	E	K	P	T	D	A	Y	G	E	L	D.	F	T	G	A	G	R	K.	Н
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2020			^~					_		~~~	mac		m00			-	.m.~m	COM	<b></b>
ACAG																			
S	N	F	L	R	L	S	D	R	_	D	P	A	A	V	_	S	L	V.	T
		370						_	90						41	-			
CACG					CCG	-		_											
R	T	W	G	F	R	A	₽	N	_	V	V	S	V	L	G	G	S	G	G
	4	130						4	50						47	0			
GCCC	CGT	CTC	CCA	GAC	CTG	GCT	GCA	GGA	CCT	GCT	GCG	TCG	TGG	GCT	GGT	GCG	GGC	TGC	CC
P	V	L	Q	T	W	L	Q	D	L	L	R	R	G	L	V	R	A	A	Q
	4	190						5	10						53	0			
AGAG	CAC	\GG!	4GC	CTG	GAT	TGT	CAC	TĢG	GGG	TCT	GCA	CAC	GGG	CAT	CGG	CCG	GCA	TGT	TG
s	T	G	A	W	I	V	T	G	G	L	H	T	G	I	G	R	H	V	G
	5	550						5	70						59	0			
GTGT	GGCI	GT	ACG	GGA	CCA	TCA	GAT	GGC	CAG	CAC	TGG	GGG	CAC	CAA	GGT	GGT	GGC	CAT	GG
V	A	v	R	D	Н	Q	M	A	s	T	G	G	T	K	v	v	A	M	G
	. (	510						6	30						65	0			
GTGT	GGC	ccc	CTG	GGG	TGT	GGT	CCG	GAA	TAG	AGA	CAC	CCT	CAT	CAA	ccc	CAA	GGG	CTC	GT
v	A	Þ	W	G	V	v	R	N	R	D	т	L	I	N	P		G,		F
		570	••	_	•	•			90	_	-	_	_	•	71				
TCCC		_	מיזיב	CCG	CTC	cce	cee			CCA	CCA	ccc	CCT	CCA	. –		ССТ	CCA	СT
P	A		Y	R	W	R		D		E	D	G	V	0	F	P	L	D	Y
		730	*	1	**	11	G		50	בו	ט	G	٧	v	77	_		D	•
2022				~mm			<b>~</b> ~~			~~~	~~ ~			<b>о</b> то		-			<b>C</b> 2
ACAA																			
N	Y	S	Α	F	F	L	V	D	D	G	T	H	G	С	L	G	G	E	N
		90							10						83				
ACCG	CTTC	CGC	CTT	GCG	CCT	GGA	GTC	CTA	CAT	CTC	ACA	GCA	.GAA	GAC	GGG	CGT	GGG	AGG	GA
R	F	R	L	R	L	E	s	Y	I	s	Q	Q	K	T	G	V	G	G	T
	8	350						8	70				•		89	0			
CTGG	TTAA	GAC	CAT	ccc	TGT	CCT	GCT	CCT	CCT	GAT	TGA	TGG	TGA	TGA	GAA	GAT	GTT	GAC	GC
G	1	D	I	P	V	L	L	L	L	I	D	G	D	E	K	M	L	T	R
	9	10						9.	30						95	0			
GAAT	AGAG	AAC	CGC	CAC	CCA	GGC'	TCA	GCT	CCC	ATG	TCT	CCT	CGT	GGC	TGG	CTC	AGG	GGG	AG
I	E					A		L						Α		s			A
-	_	70	••	•	×	••	¥		90	•	_	_	-		101	_	•	•	
CTGC	-	-	, Cm	200	CC»	~ 7\	~~m	-		רא רי	ערט הייט	cec	ددد			-	GGC	አርC	CA
A	D	_	Ţ,	A	E	T	L		D	T	Ţ	A	P	_	_	G	G	A	K
		30	_				_	10							107				
GGCA	AGGC	:GAA	GC	CCG	AGA!	rcg	TAP	CAG	GCG'	l'TT	CTT	TCC	CAA	AGG	GGA	CCT	TGA	GGT	CC

Fig. 9 / continu: n 1

QGEARDRIRRFFPKGDLEVL 1110 TGCAGGCCCAGGTGGAGAGGATTATGACCCGGAAGGAGCTCCTGACAGTCTATTCTTCTG Q A Q V E R I M T R K E L L T V Y S S E 1150 1170 AGGATGGGTCTGAGGAATTCGAGACCATAGTTTTGAAGGCCCTTGTGAAGGCCTGTGGGA DGSEEFETIVLKALVKACGS 1250 1230 GCTCGGAGGCCTCAGCCTACCTGGATGAGCTGCGTTTGGCTGTGGCTTGGAACCGCGTGG S E A S A Y L D E L R L A V A W N R V D 1290 1310 ACATTGCCCAGAGTGAACTCTTTCGGGGGGACATCCAATGGCGGTCCTTCCATCTCGAAG I A Q S E L F R G D I Q W R S F H L E A 1330 1350 CTTCCCTCATGGACGCCCTGCTGAATGACCGGCCTGAGTTCGTGCGCCTTGCTCATTTCCC SLMDALLNDRPEFVRLLISH 1390 1410 r — 1430 ACGCCTCAGCCTGGGCCACTTCCTGACCCCGATGCGCCCTGGCCCAACTCTACAGCGCGG G L S L G R F L T P M R L A Q L Y S A A 1450 1470 1490 CGCCTCCAACTCGCTCATCCGCAACCTTTTGGACCAGGCGTCCCACAGCGCAGGCACCA P S N S L I R N L L D Q A S H S A G T K 1530 AAGCCCCAGCCCTAAAAGGGGGAGCTGCGGAGCTCCGGCCCCTGACGTGGGGCATGTGC APALKGGAAELRPPDVGHVL 1570 1590 1610 TGAGGATGCTGCTGGGAAGATGTGCGCGCCGAGGTACCCCTCCGGGGCGCCCTGGGACC RMLLGKMCAPRYPSGGAWDP 1670 1.630 1650 CTCACCCAGGCCAGGGCTTCGGGGAGAGCATGTATCTGCTCTCGGACAAGGCCACCTCGC H P G Q G F G E S M Y L L S D K A T S P 1690 1710 1730 CGCTCTCGCTGGATGCTGGCCTCGGGCAGGCCCCCTGGAGCGACCTGCTTCTTTGGGCAC LSLDAGLGQAPWSDLLLWAL 1770 1790 TGTTGCTGAACAGGGCACAGATGGCCATGTACTTCTGGGAGATGGGTTCCAATGCAGTTT L L N R A Q M A M Y F W E M G S N A V S ำลาก 1830 1850 CCTCAGCTCTTGGGGCCTGTTTGCTGCTCCGGGTGATGGCACGCCTGGAGCCTGACGCTG S A L G A C L L R V M A R L E P D A E 1910 1890 AGGAGGCAGCACGGAGGAAAGACCTGGCGTTCAAGTTTGAGGGGATGGGCGTTGACCTCT E A A R R K D L A F K F E G M G V D L F 1950 1970 TTGGCGAGTGCTATCGCAGCAGTGAGGTGAGGGCTGCCCGCCTCCTCCTCCGTCGCTGCC G E C Y R S S E V R A A R L L L R R C P 2010 CGCTCTGGGGGGATGCCACTTGCCTCCAGCTGGCCATGCAAGCTGACGCCCGTGCCTTCT LWGDATCLQLAMQADARAFF 2070 2090 TTGCCCAGGATGGGGTACAGTCTCTGCTGACACAGAAGTGGTGGGGAGATATGGCCAGCA A Q D G V Q S L L T Q K W W G D M A S T 2130 2150 CTACACCCATCTGGGCCCTGGTTCTCGCCTTCTTTTGCCCTCCACTCATCTACACCCGCC T P I W A L V L A F F C P P L I Y T R L 2170 2190 2210 TCATCACCTTCAGGAAATCAGAAGAGGAGCCCACACGGGAGGAGCTAGAGTTTGACATGG I T F R K S E E P T R E E L E F D M D 2250 2270 ATAGTGTCATTAATGGGGAAGGGCCTGTCGGGACGGCGGACCCAGCCGAGAAGACGCCGC SVINGEGPVGTADPAEKTPL 2290 2310 2330

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Fig. 9 / continue in 2

G V P R Q S G R P G C C G G R C G G R R 2370 2390 2350 GGTGCCTACGCCGCTGGTTCCACTTCTGGGGCGTGCCGGTGACCATCTTCATGGGCAACG CLRRWFHFWGVPVTIFMGNV 2430 TGGTCAGCTACCTGCTGCTGCTGCTTTTCTCGCGGGTGCTGCTCGTGGATTTCCAGC V S Y L L F L L F S R V L L V D F Q P 2470 2490 CGCGCCCCGGCTCCTGGAGCTGCTGTTTTTTCTGGGCTTTCACGCTGCTGTGCG APPGSLELLYFWAFTLLCE 2550 2570 AGGAACTGCGCCAGGGCCTGAGCGGAGGCGGGGGGCAGCCTCGCCAGCGGGGCCCCCGGGC E L R Q G L S G G G G S L A S G G P G P 2630 2590 2610 CTGGCCATGCCTCACTGAGCCAGCGCCTGCGCCTCTACCTCGCCGACAGCTGGAACCAGT G H A S L S Q R L R L Y L A D S W N Q C 2670 2690 2650 GCGACCTAGTGGCTCTCACCTGCTTCCTCCTGGGCGTGGGCTGCCGGCTGACCCCGGGTT D L V A L T C F L L G V G C R L T P G L 2750 2730 TGTACCACCTGGGCCGCACTGTCCTCTGCATCGACTTCATGGTTTTCACGGTGCGGCTGC Y H L G R T V L C I D F M V F T V R L L 2770 2790 2810 TTCACATCTTCACGGTCAACAAACAGCTGGGGCCCAAGATCGTCATCGTGAGCAAGATGA HIFTVNKQLGPKIVIVSKMM 2850 TGAAGGACGTGTTCTTCTTCTTCTTCCTCGGCGTGTGGCTGGTAGCCTATGGCGTGG K D V F F F L F F L G V W L V A Y G V A 2930 2910 2890 CCACGGAGGGGCTCCTGAGGCCACGGGACAGTGACTTCCCAAGTATCCTGCGCCGCGTCT TEGLLRPRDSDFPSILRRVF 2970 TCTACCGTCCCTACCTGCAGATCTTCGGGCAGATTCCCCAGGAGGACATGGACGTGGCCC YRPYLQIFGQIPQEDMDVAL 3050 3030 TCATGGAGCACAGCAACTGCTCGTCGGAGCCCGGCTTCTGGGCACACCCTCCTGGGGCCC MEHSNCSSEPGFWAHPPGAQ 3090 3110 AGGCGGCACCTGCGTCTCCCAGTATGCCAACTGGCTGGTGGTGCTCCTCGTCATCT AGTCVSQYANWLVVLLLVIF 3130 3150 3170 TCCTGCTCGTGGCCAACATCCTGCTGGTCAACTTGCTCATTGCCATGTTCAGTTACACAT LLVANILLVNLLIAMFSYTF 3210 3230 TCGGCAAAGTACAGGGCAACAGCGATCTCTACTGGAAGGCGCAGCGTTACCGCCTCATCC G K V Q G N S D L Y W K A Q R Y R L I R 3270 3290 3250 GGGAATTCCACTCTCGGCCCGCGCTGGCCCCGCCCTTTATCGTCATCTCCCACTTGCGCC E F H S R P A L A P P F I V I S H L R L 3330 3350 TCCTGCTCAGGCAATTGTGCAGGCGACCCCGGAGCCCCAGCCGTCCTCCCCGGCCCTCG L L R Q L C R R P R S P Q P S S P A L E 3370 3390 3410 AGCATTTCCGGGTTTACCTTTCTAAGGAAGCCGAGCGGAAGCTGCTAACGTGGGAATCGG H F R V Y L S K E A E R K L L T W E S V 3430 3450 TGCATAAGGAGAACTTTCTGCTGGCACGCGCTAGGGACAAGCGGGAGAGCGACTCCGAGC H K E N F L L A R A R D K R E S D S E R 3530 3510 GTCTGAAGCGCACGTCCCAGAAGGTGGACTTGGCACTGAAACAGCTGGGACACATCCGCG LKRTSQKVDLALKQLGHIRE

**GGAAAAAAAAAAAAAA** 

Fig. 9 / continua 1 3 3550 3570 3590 AGTACGAACAGCGCCTGAAAGTGCTGGAGCGGGAGGTCCAGCAGTGTAGCCGCGTCCTGG Y E Q R L K V L E R E V Q Q C S R V L G 3630 3650 GGTGGGTGGCCGAGGCCCTGAGCCGCTCTGCCTGCCCCCAGGTGGGCCGCCACCCC WVAEALSRSALLPPGGPPPP 3710 3670 3690 CTGACCTGCCTGGGTCCAAAGACTGAGCCCTGCTGGCGGACTTCAAGGAGAAGCCCCCAC D L P G S K D * 3730 3770 3750 AGGGGATTTTGCTCCTAGAGTAAGGCTCATCTGGGCCTCGGCCCCGCACCTGGTGGCCT 3790 3810 3830 TGTCCTTGAGGTGAGCCCCATGTCCATCTGGGCCACTGTCAGGACCACCTTTGGGAGTGT 3870 3890 CATCCTTACAAACCACAGCATGCCCGGCTCCTCCCAGAACCAGTCCCAGCCTGGGAGGAT 3910 3950 CAAGGCCTGGATCCCGGGCCGTTATCCATCTGGAGGCTGCAGGGTCCTTGGGGTAACAGG 3970 3990 4010 GACCACAGACCCCTCACCACTCACAGATTCCTCACACTGGGGAAATAAAGCCATTTCAGA 4030

MVVPEKEQSWIPKIFKKKTCTTFIVDSTDPGGTLCQCGRPRTAHPAVAMEDAFGAAVVTVWDSDAHTTEKPTDAYELDFTGAGRKH
SNFLRLSDRTDPAAVYSLVTRTWGFRAPNLVVSVLGGSGGFVLQTWLQDLLRRGLVRAAQSTGAWIVTGGLHTGIGRHVGVAVRDH
QMASTGGTKVVAMGVAPWGVVRNRDTLINPKGSFPARYRWRGDPEDGVQFPLDYNYSAFFLVDDGTHGCLGGENRFRLRLESYISQ
QKTGVGGTGIDIPVLLLLIDGDEKMLTRIENATQAHVPCLLVAGSRGLGMPGGTLEAHLAQDGDHKANQSTNQLLLPKDLSLQPVE
SIDRKTLQSYSERLAVAWNRVDIAQSELFRGDIQWRSFHLEASLMDALLNDRPEFVRLLISHGLSLGHFLTPMRLAQLYSAAPSNS
LIRNLLDQASHSAGTKAPALKGGAAELRPPDVGHVLRMLLGKMCAPRYPSGGAWDPHPGQGFGESMYLLSDKATSPLSLDAGLGQA
PWSDLLLWALLLNRAQMAMYFWEMGSNAVSSALGACLLLRVMARLEPDAEEAARRKDLAFKFEGMGVDLFGECYRSSEVRAARLLL
RRCPLWGDATCLQLAMQADARAFFAQDGVQSLLTQKWWGDMASTTPIWALVLAFFCPPLIYTRLITFRKSEEEPTREELEFDMDSV
INGEGPVGTADPAEKTPLGVPRQSGRPGCCGGRCGGRRCLRRWFHFWGVPVTIFMGNVVSYLLFLLLFSRVLLVDFQPAPPGSLEL
LLYFWAFTLLCEELRQGLSGGGGSLASGGPGPGHASLSQRLRLYLADSWNQCDLVALTCFLLGVGCRLTPGLYBLGRTVLCIDFMV
FTVRLLHIFTVNKQLGFKIVIVSKMMKDVFFFLFFLGVWLVAYGVATEGLLRPRDSDFPSILRRVFYRPYLQIFGQIPQEDMDVAL
MEHSNCSSEPGFWAHPFGAQAGTCVSQYANWLVVLLLVIFLLVANILLVNLLIAMFSYTFGKVQGNSDLYWKAQRYRLIREFHSRP
ALAPPFIVISHLRLLLRQLCRRPRSPQPSSPALEHFRVYLSKEAERKLLTWESVHKENFLLARARDKRESDSERLKRTSQKVDLAL
KQLGHIREYEQRLKVLEREVQQCSRVLGWVAEALSRSALLPPGGPPPPDLPGSKD

в.

10 30 50 ATCCAATGGCGGTCCTTCCATCTGAAGCTTCCCTCATGGACGCCCTGCTGAATGACCGG 70 90 110 CCTGAGTTCGTGCGCTTGCTCATTTCCCACGGCCTCAGCCTGGGCCACTTCCTGACCCCG 130 150 170 ATGCGCCTGGCCCAACTCTACAGCGCGCGCCCTCCAACTCGCTCATCCGCAACCTTTTG 190 210 230 GACCAGGCGTCCCACAGCGCAGGCACCAAAGCCCCAGCCCTAAAAGGGGGAGCTGCGGAG 250 270 290 CTCCGGCCCCTGACGTGGGGCATGTGCTGAGGATGCTGCTGGGGAAGATGTGCGCGCCG 310 330 350 AGATGTATCTGCTCTCGGACAAGGCCACCTCGCCGCTCTCGCTGGATGCTGGCCTCGGGC YLLSDKATSPLSLDAGLGQ 390 410 AGGCCCCTGGAGCGACCTGCTTCTTTGGGCACTGTTGCTGAACAGGGCACAGATGGCCA PWSDLLLWALLINRAQMAM 430 470 450 TGTACTTCTGGGAGATGGGTTCCAATGCAGTTTCCTCAGCTCTTGGGGCCTGTTTGCTGC YFWEMGSNAVSSALGACLLL

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Fig. 9 / continua 14

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GGGG	CG'	rgcc	GGT	'GAC	CAT	CTT	CAT	GGGCAZ	CGI	'GGI	CAG	CTA	CCI	GCTGT	rcci	GCT	GC
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TGCT L	TCTA Y	L150 ATTT F L210	CTG W	GGC A	TTT F	CAC T	GCT L	1170 GCTGTG L C 1230	GCGA E	igga e	ACT L	GCG R	CCA Q	1190 GGGCC' G L	rgac S	G G	AG G
TGCT L	CTX Y SGG(	L150 ATTT F L210	CTG W	GGC A	TTT F	CAC T	GCT L	1170 GCTGTG L C 1230	GCGA E	igga e	ACT L	GCG R	CCA Q	1190 AGGGCC G L 1250 CACTGAG	rgac S	G G	AG G
TGCT	TCTA Y SGG(	L150 ATTT F L210 ECAG	CTG W CCT	GGC A	TTT F CAG	CAC T CGG	GGG	1170 GCTGTG L C 1230 CCCCGG	E E GCC	GGA E TGG	ACT L SCCA	GCG R TGC	CTC	1190 AGGGCC G L 1250 CACTGAG	rgac s sccz	G G	AG G
TGCT L GCGG	TCTX Y SGG(	F L210 ECAG S	CTG W CCT L	GGC A CGC A	TTT F CAG S	CAC T CGG	EGGE L EGGE G	1170 GCTGTG L C 1230 CCCCGG P G 1290	E GGCC P	GGA E TGG G	ACT L SCCA H	GCG R TGC A	CCA Q CTC	1190 AGGGCC G L 1250 CACTGAG	rgag S SCC# Q	G G AGCG R	AG G CC L
TGCT L GCGG	TCTX Y SGG(	L150 ATTT F L210 ECAG S L270	CTG W CCT L	GGC A CGC A	TTT F CAG S	CAC T CGG	EGGE L EGGE G	1170 GCTGTG L C 1230 CCCCGG P G 1290	E GGCC P	GGA E TGG G	ACT L SCCA H	GCG R TGC A	CTC S	1190 AGGGCC G L 1250 CACTGA L S 1310	rgag S SCC# Q	G G AGCG R	AG G CC L
TGCT  GCGG	CTI Y SGG( G G CCT	L150 ATTT F L210 ECAG S L270	CTG W CCT L	GGC A CGC A	TTT F CAG S	CAC T CGG G CAG	GGG GGG G	1170 GCTGTG L C 1230 CCCCGG P G 1290 GAACCA	GCGA E GCC P	E TGG G	ACT L SCCA H	GCG R TGC A	CTC S	1190 AGGGCC G L 1250 CACTGA L S 1310	rgag s gcc <i>i</i> Q	G G AGCG R GCTT	AG G CC L
TGCT L GCGG G	FCTI Y SGGGG G GCCT	L150 ATTT F L210 ECAG S L270 FCTA Y	CTG W CCT L CCT	GGC A CGC A	TTT F CAG S CGA	CAC T CGG G CAG	GGG GGG GCTG	1170 GCTGTG L C 1230 CCCCGG P G 1290 GAACCA N Q 1350	GCGA E GCC P LGTG C	E TGG G CGA	L CCT L	GCG R TGC A V	CTC S GGC	1190 AGGGCC G L 1250 CACTGAG L S 1310 CTCTCAG L T 1370	rgac s ccr c	GCGG G AGCG R SCTT	AG CC L
TGCT L GCGG G TGCG	CCTA  SGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	L150 ATTT F L210 SCAG S L270 FCTA Y L330 SCGT	CTG W CCT L CCT L	GGC A CGC A CGC	CAG S CGA D	CAC T CGG G CAG S	GGGG GGGG GGGG W	1170 GCTGTG L C 1230 CCCCGG P G 1290 GAACCA N Q 1350 CCCCGGG	GCGA E GCC P AGTG C	GGA E G G GCGA D	ACT L CCA L CCA	GCG R TGC A AGT V	CTC S GGGC A	1190 GGGGCCC G L 1250 CACTGAC L S 1310 CTCTCAC L T 1370 GCCGCAC	rgad s sccr Q ccto c	GCGG G AGCG R F GCTT F	AG G CC L CC
TGCT L GCGG G	Y SGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	F L210 SCAG S L270 FCTA Y L330 SCGT	CTG W CCT L CCT L	GGC A CGC A CGC	CAG S CGA D	CAC T CGG G CAG S	GGGG GGGG GGGG W	1170 GCTGTG L C 1230 CCCCGGG P G 1290 GAACCA N Q 1350 CCCGGG	GCGA E GCC P AGTG C	GGA E G G GCGA D	ACT L CCA L CCA	GCG R TGC A AGT V	CTC S GGGC A	1190 GGGCC' G L 1250 CACTGAC L S 1310 CTCTCAC L T 1370 GCCGCAC	rgac s ccr c	GCGG G AGCG R F GCTT F	AG G CC L CC
TGCT L GCGG G TGCG R	Y Y Y GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	E150 ATTT F L210 SCAG S L270 FCTA Y L330 SCGT	CTG W CCT L CCT L	GGC A CGC A CTG	TTT F CAG S CGA D CCG R	CAG T CGG G CAG S GCT L	GGGG GGGG GGGG W	1170 GCTGTG L C 1230 CCCCGGG P G 1290 GAACCA N Q 1350 CCCGGG	GCGA E GCC P AGTG C TTT	GGA E G G CGA D	ACT L CCT L CCA	GCG R TGC A AGT V	CTC S GGG A	1190 GGGGCC' G L 1250 CACTGAC L S 1310 CTCTCAC L T 1370 GCCGCAC R T 1430	rgad S GCCZ Q CCTG C	GCGG GAGCG R GCTT F	AG G CC L CC CT
TGCT L GCGG R TGCCT L GCAT	Y Y SEGGEOGE G G G T T T T T T T T T T T T T T T T	1150 F 1210 CAG S 1270 CCTA Y 1330 CCTC V 1390	CTG W CCT L CCT L GGG G	GGGC A CGC A CTG CTG	TTT F CAG S CGA D CCG R	CAC T CGG G CAG S GCT L CAC	GGTC	1170 GCTGTG L C 1230 CCCCGG P G 1290 GAACCA N Q 1350 CCCGGG P G 1410	GCGA E GGCC P AGTG C TTTT L	E CGA D CTA	ACT L GCCA H ACCT L ACCA H	GCG R TGC A AGT V CCT L	CCCA Q CTC S GGGC A GGGG	1190 GGGGCC' G L 1250 CACTGAG L S 1310 CTCTCAG L T 1370 GCCGCAG R T 1430	rgag s ccr c ccr c	GCGG GAGCG R GCTT F	AG G CC L CT C
TGCT L GCGG G TGCG R	Y Y SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECOND SECON	L150 ATTT F L210 ECAG S L270 FCTA Y L330 ECGT V L390 ACTT	CTG W CCT L CCT L GGG G	GGGC A CGC A CTG CTG	TTT F CAG S CGA D CCG R	CAC T CGG G CAG S GCT L CAC	GGTC	1170 GCTGTG L C 1230 CCCCGG P G 1290 GAACCA N Q 1350 CCCGGG P G 1410 GCGGCT R L	GCGA E GGCC P AGTG C TTTT L	E CGA D CTA	ACT L GCCA H ACCT L ACCA H	GCG R TGC A AGT V CCT L	CCCA Q CTC S GGGC A GGGG	1190 GGGGCC' G L 1250 CACTGAG L S 1310 TCTCAG L T 1370 GCCGCAG R T 1430 CGGTCAG V N	rgag s ccr c ccr c	GCGG GAGCG R GCTT F	AG G CC L CT C
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GG D CG G E

Fig. 9 / continuation 5

P G F W A H P P G A Q A G T C V S Q Y A 1790 1770 1750 CCAACTGGCTGGTGGTGCTCCTCGTCATCTTCCTGCTCGTGGCCAACATCCTGCTGG N W L V V L L L V I F L L V A N I L L V 1850 1810 1830 TCAACTTGCTCATTGCCATGTTCAGTTACACATTCGGCAAAGTACAGGGCAACAGCGATC N L L I A M F S Y T F G K V Q G N S D L 1890 1910 TCTACTGGAAGGCGCAGCGTTACCGCCTCATCCGGGAATTCCACTCTCGGCCCGCGCTGG YWKAQRYRLIREFHSRPALA 1970 1930 1950 CCCCGCCTTTATCGTCATCTCCCACTTGCGCCTCCTGCTCAGGCAATTGTGCAGGCGAC P P F I V I S H L R L L L R Q L C R R P 2030 2010 CCCGGAGCCCCAGCCGTCCTCCCCGGCCCTCGAGCATTTCCGGGTTTACCTTTCTAAGG R S P Q P S S P A L E.H F R V Y L S K E 2090 2050 2070 **AAGCCGAGCGGAAGCTGCTAACGTGGGAATCGGTGCATAAGGAGAACTTTCTGCTGGCAC** AERKLLTWESVHKENFLLA.R 2150 2130 2110 GCGCTAGGGACAAGCGGGAGAGCGACTCCGAGCGTCTGAAGCGCACGTCCCAGAAGGTGG A R D K R E S D S E R L K R T S Q K V D 2190 ACTTGGCACTGAAACAGCTGGGACACATCCGCGAGTACGAACAGCGCCTGAAAGTGCTGG LALKQLGHIREYEQRLKVLE 2270 - 2250 R E V Q Q C S R V L G W V A E A L S R S 2330 2310 ALLPPGGPPPDLPGSKD* 2370 2390 -2350CCCTGCTGGCGGACTTCAAGGAGAAGCCCCCACAGGGGATTTTGCTCCTAGAGTAAGGCT 2430 CATCTGGGCCTCGGCCCCGCACCTGGTGGCCTTGTCCTTGAGGTGAGCCCCATGTCCAT 2470 2490 CTGGGCCACTGTCAGGACCACCTTTGGGAGTGTCATCCTTACAAACCACAGCATGCCCGG 2550 CTCCTCCCAGAACCAGTCCCAGCCTGGGAGGATCAAGGCCTGGATCCCGGGCCGTTATCC 2630 2610 ATCTGGAGGCTGCAGGGTCCTTGGGGTAACAGGGACCACAGACCCCTCACCACTCACAGA 2650 2670 2690 

MYLLSDKATSPLSLDAGLGQAPWSDLLLWALLLNRAQMAMYFWEMGSNAVSSALGACLLLRVMARLEPDAEEAARRKDLAFKFEGM GVDLFGECYRSSEVRAARLLLRRCPLWGDATCLQLAMQADARAFFAQDGVQSLLTQKWWGDMASTTPIWALVLAFFCPPLIYTRLI TFRKSEEEPTREELEFDMDSVINGEGPVGTADPAEKTPLGVPRQSGRPGCCGGRCGGRRCLRRWFHFWGVPVTIFMGNVVSYLLFL LLFSRVLLVDFQPAPPGSLELLLYFWAFTLLCEELRQGLSGGGGSLASGGPGPGHASLSQRLRLYLADSWNQCDLVALTCFLLGVG CRLTPGLYHLGRTVLCIDFMVFTVRLLHIFTVNKQLGPKIVIVSKMMKDVFFFLFFLGVWLVAYGVATEGLLRPRDSDFPSILRRV FYRPYLQIFGQIPQEDMDVALMEHSNCSSEPGFWAHPPGAQAGTCVSQYANWLVVLLLVIFLLVANILLVNLLIAMFSYTFGKVQG NSDLYWKAQRYRLIREFHSRPALAPPFIVISHLRLLLRQLCRRPRSPQPSSPALEHFRVYLSKEAERKLLTWESVHKENFLLARAR DKRESDSERLKRTSQKVDLALKQLGHIREYEQRLKVLEREVQQCSRVLGWVAEALSRSALLPPGGPPPPDLPGSKD

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30 ATTAAAGTTTATAAAACAGTGGCTGGATGGTTGGAGGATGCAGGTGGACAGAAGACGTGG MVGGCRWTEDVE 90 110 AGCCTGCAGAAGTAAAGGAAAAGATGTCCTTTCGGGCAGCCAGGCTCAGCATGAGGAACA PAEVKEKMSFRAARLSMRNR 150 170 GAAGGAATGACACTCTGGACAGCACCCGGACCCTGTACTCCAGCGCGTCTCGGAGCACAG RNDTLDSTRTLYSSASRSTD 210 230 ACTTGTCTTACAGTGAAAGCGCCAGCTTCTACGCTGCCTTCAGGACACAGACGTGCCCAA LSYSESASFYAAFRTQTCPI 250 270 290 TCATGGCTTCTTGGGGACTTGGTGAATTTTATTCAAGCAAATTTTAAGAAACGAGAATGTG M A S W D L V N F I Q A N F K K R E C V 330 TCTTCTTTACCAAAGATTCCAAGGCCACGAGAATGTGTGCAAGTGTGGCTATGCCCAGA F F T K D S K A T E N V C K C G Y A Q S 370 390 410 GCCAGCACATGGAAGGCACCCAGATCAACCAAAGTGAGAAATGGAACTACAAGAAACACA Q H M E G T Q I N Q S E K W N Y K K H T 430 450 470 CCAAGGAATTTCCTACCGACGCCTTTGGGGATATTCAGTTTGAGACACTGGGGAAGAAAG K E F P T D A F G D I Q F E T L G K K G 490 510 GGAAGTATATACGTCTGTCCTGCGACACGGACGCGGAAATCCTTTACGAGCTGCTGACCC K Y I R L S C D T D A E I L Y E L L T Q AGCACTGGCACCTGAAAACACCCAACCTGGTCATTTCTGTGACCGGGGGCGCCCAAGAACT HWHLKTPNLVISVTGGAKNF 630 TCGCCCTGAAGCCGCGCATGCGCAAGATCTTCAGCCGGCTCATCTACATCGCGCAGTCCA A L K P R M R K I F S R L I Y I A Q S K 690 **AAGGTGCTTGGATTCTCACGGGAGGCACCCATTATGGCCTGATGAAGTACATCGGGGAGG** G A W I L T G G T H Y G L M K Y I G E V 730 750 TGGTGAGAGATAACACCATCAGCAGGAGTTCAGAGGAGAATATTGTGGCCATTGGCATAG V R D N T I S R S S E E N I V A I G I A 810 830 CAGCTTGGGGCATGGTCTCCAACCGGGACACCCTCATCAGGAATTGCGATGCTGAGGGCT A W G M V S N R D T L I R N C D A E G Y 870 ATTTTTTAGCCCAGTACCTTATGGATGACTTCACAAGAGATCCACTGTATATCCTGGACA F L A Q Y L M D D F T R D P L Y I L D N 930 950  ${\tt ACAACCACACATTTGCTGCTCGTGGACAATGGCTGTCATGGACATCCCACTGTCGAAG}$ N H T H L L V D N G C H G H P T V E A 990 CAAAGCTCCGGAATCAGCTAGAGAAGTATATCTCTGAGCGCACTATTCAAGATTCCAACT K L R N Q L E K Y I S E R T I Q D S N Y 1030 1050 1070 ATGGTGGCAAGATCCCCATTGTGTTTTTGCCCAAGGAGGTGGAAAAGAGACTTTGAAAG G G K I P I V C F A Q G G G K E T L K A 1110 CCATCAATACCTCCATCAAAAATAAAATTCCTTGTGTGGTGGTGGAAGGCTCGGGCCAGA INTSIKNKIPCVVVEGSGQI 1150 1170 TCGCTGATGTGATCGCTAGCCTGGTGGAGGTGGAGGATGCCCTGACATCTTCTGCCGTCA A D V I A S L V E V E D A L T S S A V K 1210 1230 1250

Fig. 10 / continur≃nn 1

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Fig. 10 / continuation 2

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N E Q I 3130 TGTTCGGCCAGO F G Q V	R W	R W	i ACGT	F R 3150 GGATGO D G	S STAC	V CACG	I Y	E ACT	PY 3170 PTGCCCA AH	F	A SCAC	M
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TCACTGGGAATC	R W GTGCC V P	R W	ACGT V	F R 3150 PGGATGO D G 3210 PGTGTGT	S T T TGGA	V CACG T SCTG	I Y TATG <i>I</i> Y D	E ACTI F AGCI	P Y 3170 PTGCCCA A H 3230 ACAACCA	L C C	A CAC T	M CT F
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N E Q I 3130 TGTTCGCCAGC F G Q V 3190 TCACTGGAATC T G N I 3250 TCCCCGAGTGGA P E W 3310 TGGTCAACCTGG V N L 3370 ACCAGGTCTGGA Q V W I 3430 TCCCCTTCCCC P F P I 3490 GTTGCTGCAAGG	TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TO	R W CAGTO S D CAAGO K F CATCO I F CGCCA A M CCAGA Q F CGTCI V F	ACGTA TGGGA TGGGA TGGGA TGGGA TGGGA TGGGA TGGGA	F R 3150 GGATGC D G 3210 CGTGTGT C V 3270 CGGTGTC V C 3330 CTTCCT F L 3450 CTTACTT Y F 3510 GGTCTTC	S TGGAN T GGATO T TGGTO V TCTAO Y	V CACG T GCTGC L CTACC Y GCAG Q CATGC	TATGA Y D GATGA D E ATGTT M L GGCAC G T GAGTA E Y GTGGT	E ACTION OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUN	P Y 3170  TTGCCCI A H 3230  ACAACC N L 3290  CCACCAI T N 3350  FCCAGGI Q E 3410  GCAGCCC S R 3470  AGAAGTC K C 3530  GGTTTA	L ACTO C C P ACAT I AGAZ N F F CCC	A GCAC  R CCCCI L ACAP  N CCAP  K CCCAP  K ACAP  K ATGI	M CCT F GGT F CGC L ATG D AGT C TGT
N E Q I 3130  TGTTCGCCAGC F G Q Y 3190  TCACTGGAATC T G N I 3250  TCCCCGAGTGGA P E W 3310  TGGTCAACCTGG V N L 3370  ACCAGGTCTGGA Q V W I 3430  TCCCCTTCCCC P F P I 3490  GTTGCTGCAAGC C C K I	TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TOTAL  TO	R W CAGTO S D CAAGO K F CATCO I F CGCCA A M CCAGA Q F CGTCI V F	ACGTA TGGGA TGGGA TGGGA TGGGA TGGGA TGGGA TGGGA	F R 3150 CGGATGC D G 3210 CGTGTGT C V 3270 CGGTGTC V C 3330 CTTGCT F L 3450 CTTACT Y F 3510 CGTCTT S S	S TGGAN T GGATO T TGGTO V TCTAO Y	V CACG T GCTGC L CTACC Y GCAG Q CATGC	TATGA Y D GATGA D E ATGTT M L GGCAC G T GAGTA E Y GTGGT	E ACTION OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUNTS OF ACCOUN	P Y 3170 TTGCCCA A H 3230 ACAACC N L 3290 CCACCAI T N 3350 FCCAGGGI Q E 3410 GCAGGCC S R 3470 AGAAGTC K C 3530 GGTTTA	L ACTO C C P ACAT I AGAZ N F F CCC	A GCAC  R CCCCI L ACAP  N CCAP  K CCCAP  K ACAP  K ATGI	M CCT F GGT F CGC L ATG D AGT C TGT
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Fig. 10 / continue in 3

MVGGCRWTEDVEPAEVKEKMSFRAARLSMRNRRNDTLDSTRTLYSSASRSTDLSYSESASFYAAFRTQTCPIMASWDLVNFIQANF
KKRECVFFTKDSKATENVCKCGYAQSQHMEGTQINQSEKWNYKKHTKEFPTDAFGDIQFETLGKKGKYIRLSCDTDAEILYELLTQ
HWHLKTPNLVISVTGGAKNFALKPRMRKIFSRLIYIAQSKGAWILTGGTHYGLMKYIGEVVRDNTISRSSEENIVAIGIAAWGMVS
NRDTLIRNCDAEGYFLAQYLMDDFTRDPLYILDNNHTHLLLVDNGCHGHPTVEAKLRNQLEKYISERTIQDSNYGGKIPIVCFAQG
GGKETLKAINTSIKNKIPCVVVEGSGQIADVIASLVEVEDALTSSAVKEKLVRFLPRTVSRLPEEETESWIKWLKEILECSHLLTV
IKMEEAGDEIVSNAISYALYKAFSTSEQDKDNWNGQLKLLLEWNQLDLANDEIFTNDRRWEKSKPRLRDTIIQVTWLENGRIKVES
KDVTDGKASSHMLVVLKSADLQEVMFTALIKDRPKFVRLFLENGLNLRKFLTHDVLTELFSNHFSTLVYRNLQIAKNSYNDALLTF
VWKLVANFRRGFRKEDRNGRDEMDIELHDVSPITRHPLQALFIWAILQNKKELSKVIWEQTRGCTLAALGASKLLKTLAKVKNDIN
AAGESEELANEYETRAVGESTVWNAVVGADLPCGTDIASGTHRPDGGELFTECYSSDEDLAEQLLVYSCEAWGGSNCLELAVEATD
QHFIAQPGVQNFLSKQWYGEISRDTKNWKIILCLFIIPLVGCGFVSFRKKPVDKHKKLLWYYVAFFTSPFVVFSWNVVFYIAFLLL
FAYVLLMDFHSVPHPPELVLYSLVFVLFCDEVRQGRPAAPSAGPAKPTPTRNSIWPASSTRSPGSRSRHSFHTSLQAEGASSGLGQ
PRKGWTFKNLEMVDISKLLMSLSVPFCTQWYVNGVNYFTDLWNVMDTLGLFYFIAGIVFRQGILRQNEQRWRWIFRSVIYEPYLAM
FGQVPSDVDGTTYDFAHCTFTGNESKPLCVELDEHNLPRFPEWITIPLVCIYMLSTNILLVNLLVAMFGYTVGTVQENNDQVWKFQ
RYFLVQEYCSRLNIPFPFIVFAYFYMVVKKCFKCCCKEKNMESSVCCEWFIHVYLGSEAAINFREGCLHPVIGSWTPGWLVWTSTR
ILTCSAGWPAAGSLSVTTHSSWVPAKSSKSQAHPDRTGRECDSASGWEGQPARWVEESVALFGHRGPVWPPTTLGITELNAPVL

в.

O L 2290 2310 2330 TGCTGGTCTATTCCTGTGAAGCTTGGGGTGGAAGCAACTGTCTGGAGCTGGCGGTGGAGG LVYSCEAWGGSNCLELAVEA 2350 2370 2390 TDQHFIAQPGVQNFLSKQWY 2430 2450 ATGGAGAGATTTCCCGAGACACCAAGAACTGGAAGATTATCCTGTGTCTGTTTATTATAC G E I S R D T K N W K I I L C L F I I P 2470 2490 CCTTGGTGGCTGTGGCTTTGTATCATTTAGGAAGAACCTGTCGACAAGCACAAGAAGC LVGCGFVSFRKKPVDK

Figure 11:

a.) Trp10b cDNA and derived amino acid sequence

		10						30						50			
AT	GAA	ATCCI	TCCI	TCC	TGT	'CCA	CAC	CATCGT	GCT	TAT	'CAG	GGA	GAA	TGT	GTG	CAA	GTGT
M	K	S F	L	P	V	H	${f T}$	I V	L	I	R	E	N	V	C	K	C
		70						90						110			
GG	CTA'	TGCCC	AGAC	CCA	GCA	CAT	GGA	AGGCAC	CCA	GAT	CAA	CCA	AAG	TGA	GAA	ATG	GAAC
G	Y	A C		0	Н	М	E	G T	0		N	0	s	E	ĸ	W	N
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CT								TCTGTC									
L	G	K K	G	K	Y	I	R	L S	C	D	${f T}$	D	A	E	I.	L	Y
		250						270						290			
GA	GCT	GCTGA	CCCA	<b>IGCA</b>	CTG	GCA	CCT	GAAAAC	ACC	CAA	CCT	GGT	CAI	TTC'	TGT	GAC	CGGG
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		430						450						470			
TA	CAT	CGGGG	AGGI	GGT	GAG.	AGA	TAA	CACCAT	CAG	CAG	GAG						
Y	I	G E	v	V	R	D	N	T I	s	R	S	s	$\mathbf{E}$	E	И	1	V
		490						510						530			
GC	CAT:	TGGCA	TAGO	AGC	TTG	GGG	CAT	GGTCTC	CAA	CCG	GGA	CAC	CCI	CAT	CAG	GAA	TTGC
Α	I	G I	A	A	W	G	M	v s	N	R	D	$\mathbf{T}$	L	I	R	N	C
		550						570						590			
GD'	דיכירי		מרידים	արդուր Մարդուր	ጥጥጥ	אמר	ררם.	GTACCT	ጥልጥ	GGA	TCA	OTT.	ראכ	AAG	AGA	TCC	ACTG
D	A	E G		F	L	A	0	Y L	M	D	D	F	т		ם	P	L
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		CCTGG						TTTGCT						CTG			
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Y	I	CTGG L D 670	N	N	Н	T	H	TTTGCT L L 690	L	V	D	N	G	CTG' C 710	H	G	H
Y	I	CTGG L D 670	N	N	Н	T	H	TTTGCT L L	L	V	D	N	G	CTG' C 710	H	G CAC	H TATT
Y	I	CTGG L D 670	N AAGC	N	Н	T	H	TTTGCT L L 690	L	V	D	N	G	CTG' C 710	H	G CAC	H
Y CC	I CAC'	CCTGG L D 670 FGTCG	N AAGC	N AAA	H GCT	T CCG	H GAA	TTTGCT L L 690 TCAGCT	L AGA	V GAA	D GTA	N TAT	G CTC	CTG' C 710	H GCG	G CAC	H TATT
Y CC P	I CACT T	CCTGG L D 670 FGTCG V E 730	n AAGC A	N AAA K	H GCT L	T CCG R	H GAA' N	TTTGCT L L 690 TCAGCT Q L	L AGA E	V GAA K	D GTA' Y	N TAT	G CTC S	CTG' C 710 TGAC E 770	H SCG R	G CAC T	H TATT I
Y CC P CA	I CACT T	CCTGG L D 670 FGTCG V E 730	N AAGC A ACTA	N AAA K	H GCT L	T CCG R	H GAA' N	TTTGCT L L 690 TCAGCT Q L 750	L AGA E	V GAA K	D GTA' Y	N TAT	G CTC S	CTG' C 710 TGAC E 770	H SCG R	G CAC T	H TATT I
Y CC P	I CACT T	CCTGG L D 670 FGTCG V E 730 FTCCA	N AAGC A ACTA	N AAA K TGG	H GCT L TGG	T CCG R CAA	H GAA' N GAT	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I	L AGA E TGT	V GAA K GTG	D GTA' Y TTT'	n Tat I TGC	G CTC S CCA	CTG' 710 TGAG T70	H GCG R AGG	G CAC T TGG	H TATT · I AAAA
Y CC(P P CA)	I CACT T AGAT D	CCTGG L D 670 FGTCG V E 730 FTCCA S N 790	N AAGC A ACTA Y	N RAAA K TGG G	H GCT L TGG	T CCG R CAA K	H GAA' N GAT I	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810	L AGA E TGT V	V GAA K GTG C	D GTA' Y TTT'	N TAT I IGC A	G CTC S CCA Q	CTG' C 710 CTGAC E 770 AGG G 830	H GCG R AGG G	G CAC T TGG G	H TATT · I AAAA K
Y CC( P CA) Q GA(	I T AGAN D	CCTGG L D 670 FGTCG V E 730 FTCCA S N 790 FTTGA	N AAGC A ACTA Y AAGC	N RAAA K TGG G	H GCT L TGG G CAA'	T CCG R CAA K TAC	H GAA' N GAT' I CTC'	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA	L AGA E TGT V AAA	V GAA K GTG C	D GTA' Y TTT' F AAT'	n Tat I TGC A	G CTC S CCA Q TTG	CTG' 710 TGAG 770 AGG2 G 830	H ECG R AGG G	G CAC T TGG G	H TATT I AAAA K GGAA
Y CC(P P CA)	I CACT T AGAT D	CCTGG L D 670 GTCG V E 730 FTCCA S N 790 FTTGA L K	N AAGC A ACTA Y AAGC	N RAAA K TGG G	H GCT L TGG	T CCG R CAA K	H GAA' N GAT I	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K	L AGA E TGT V AAA	V GAA K GTG C	D GTA' Y TTT'	N TAT I IGC A	G CTC S CCA Q	CTG' 710 TTGAC E 770 AGGG G 830 TTGTC	H GCG R AGG G	G CAC T TGG G	H TATT · I AAAA K
Y CC(P CA) Q GA(F	I T AGAT D GACT	CCTGG L D 670 GTCG V E 730 FTCCA S N 790 FTTGA L K	N AAGC A ACTA Y AAGC A	N RAAA K TGG G CAT	H GCT L TGG G CAA'	T CCG R CAA K TAC	H GAA' N GAT I CTC	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870	L AGA E TGT V AAA N	V GAA K GTG C TAA	D GTA' Y TTT' F AAT'	N TAT I TGC A ICC	G CTC S CCA Q TTG C	CTG' 710 TGAC E 770 AGG2 G 830 TGTC V 890	H ECG R AGG G G EGT	G T TGG G G GGT V	H TATT I AAAA K GGAA E
Y CC(P CA) Q GA( E	I T AGAT D GACT T	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGGCC	N AAGC A ACTA Y AAGC A	N EAAA K TGG G CAT I	H GCT L TGG G CAA' N	T CCG R CAA K TAC T	H GAA' N GAT' I CTC' S GAT'	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG	AGA E TGT V AAA N	V GAA K GTG C TAA K	GTA' Y TTT' F AAT' I	TATI IGC A ICC P	G CTC S CCA Q TTG C	CTG' C 710 TGAC E 770 AGGA G 830 TGTC V 890	H ECG R AGG G EGT V	G CAC T TGG G GGT V	H TATT I AAAA K GGAA E GACA
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Y CCO P CAA Q GAO GGO GGO	I CACT T AGAT D GACT T CTCG	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGGCC G Q	N AAGC A ACTA Y AAGC A	N RAAA TGG G CAT I	H GCT L TGG G CAA' N TGA'	T CCG R CAA K TAC T TGT V	H GAA' SAT' CTC' S GAT'	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930	L AGA E TGT V AAA N CCT	V GAA K GTG C TAA K GGT	D GTA' Y TTT' F AAT' I GGA(	TATTATTATA	G CTC S CCA Q TTG C GGA E	CTG' C 710 CTGAC E 770 AGG AGG STGTC V 890 CGGAC	H ECG R AGG G EGT V TGC	G TGG G GGT V CCT	H TATT I AAAA K GGAA E GACA T
Y CCO P CAA Q GAO GGO GGO	I CACT T AGAT D GACT T CTCG	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGGCC G Q	N AAGC A ACTA Y AAGC A	N RAAA TGG G CAT I	H GCT L TGG G CAA' N TGA'	T CCG R CAA K TAC T TGT V	H GAA' SAT' CTC' S GAT'	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S	L AGA E TGT V AAA N CCT	V GAA K GTG C TAA K GGT	D GTA' Y TTT' F AAT' I GGA(	TATTATTATA	G CTC S CCA Q TTG C GGA E	CTG' C 710 CTGAC E 770 AGG AGG STGTC V 890 CGGAC	H ECG R AGG G EGT V TGC	G TGG G GGT V CCT	H TATT I AAAA K GGAA E GACA T
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Y CCO P CAA Q GAO GGO GGO	I CACT T AGAT D GACT T CTCC	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTGA L K 850 GGCC G Q 910 CGCCG A V	N AAGC A ACTA Y AAGC A AGAT I	N CAAA CGC CGC A GGA	H GCT L TGG G CAA' N TGA' D	T CCG R CAA K TAC T TGT V	H GAA' N GATC I CTC S GATC I	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F	AGA E TGT V AAA N CCT L	V GAA K GTG C TAA K GGT V ACC	D GTA' Y TTT' F AAT' I GGAG E	TATTI TGCT A TCCT P TGGTC V CACC	G CTC S CCA Q TTG C GGA E	CTG' 710 710 TGAG 770 AGGA 830 TGTG V 890 GGA D 950	H ECG R AGG G V TGC A	G CAC T TGG G V CCT L	H TATT I AAAA K GGAA E GACA T GCCT
Y CCO P CAA Q GAO E GGO G TCT	I CACT T AGAT D SACT S FTCT S	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGGCC G Q 910 TGCGG	N AAGC A ACTA Y AAGC A I ICAA K	EAAA K TGG CAT I CGC' A	H GCT L TGGG G CAA N TGA D GAA K	T CCGG R CAAA K TACC T TGTC V GCTC L	H GAA' N GATC CTCC S GATC V	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F	L AGA E TGT V AAA N CCT L TTT	V GAA K GTG C TAA K GGT V ACC	D GTA Y TTT F AAT I GGA E CCGG	N TAT I TGC A TCC P GGT V CAC	G CTC S CCA Q CTTG C C GGA E GGT V 1	CTG' 710 TGAG 770 AGGA 830 TGTG V 890 CGGA CGTCG S	H SCG R AGG G V TGC A CCG R	G CAC T TGG G GT V CCT L GCT	H TATT I AAAA K GGAA E GACA T GCCT P
Y CCO P CAM Q GAO GAO G G G G G G G G G G G G G G G G	I CACT T AGAT D SACT T CTCG S FTTCT S	CCTGG L D 670 GTCG V E 730 FTCCA S N 790 FTTGA L K 850 GGCCG G Q 910 CGCCG A V 970 GGAGA	N AAGC A AAGC A AGAT I CAA K CTGA	N AAAA K TGG G CAT I CGC A GGAA E GAG	H GCT L TGGG G CAA N TGA D GAA K	T CCGG R CAA K TAC T TGT V GCT L	H GAA' N GAT' I CTC' S GAT' I GGT' V CAAA	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT	L AGA E TGT V AAA N CCT L TTT L	V GAA K GTG C TAA K GGT V ACC P	D GTA Y TTTT F AAT I GGA E CCG R	N TAT I TGC A TCC P CAC T	G CTC S CCA Q TTG C GGA E GGT V 1 CGA	CTG' 710 710 710 770 AGG2 830 7TGTC 890 CGGA' 0 950 CGTCC S 010 ATG'	H SCG R AGG G V TGC A CCG R	G CAC T TGG G G CT L GCT L TCA	TATT I AAAA K GGAA E GACA T GCCT P
Y CCO P CAA Q GAO E GGO G TCT	I CACT T AGAT D SACT T CTCG S FTTCT S	CCTGG L D 670 GTCG V E 730 FTCCA S N 790 FTTGA L K 850 GGCC G Q 910 FGCCG A V 970 GGAGA E T	N AAGC A AAGC A AGAT I CAA K CTGA	N AAAA K TGG G CAT I CGC A GGAA E GAG	H GCT L TGGG G CAA N TGA D GAA K	T CCGG R CAA K TAC T TGT V GCT L	H GAAT N GGAT I CCTC S GGAT V CCAAA	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L	L AGA E TGT V AAA N CCT L TTT L	V GAA K GTG C TAA K GGT V ACC P	D GTA Y TTTT F AAT I GGA E CCG R	N TAT I TGC A TCC P CAC T	G CTC S CCA Q TTG C GGA E GGT V 1 CGA E	CTG' C 710 TGAC TGAC 870 AGGA V 890 CGGA CGGA O 950 CGTC S 010 ATG	H SCG R AGG G V TGC A CCG R	G CAC T TGG G G CT L GCT L TCA	H TATT I AAAA K GGAA E GACA T GCCT P
Y CCO P CAA Q GAO G G G G G G G G G G G G G G G G G G	I CACT T AGAT D GACT T CTCG S FTCT S GGAG E	CCTGG L D 670 GTCG V E 730 TTCA S N 790 TTTGA L K 850 GGCC G Q 910 CGCCG A V 970 GGAGA E T 1030	AAGC A ACTA Y AAGC A AGAT I CCAA K CTGA	N AAAA K TGG G CAT I CGC A GGAA E GAAG	H GCT L TGGG G CAAA N TGAA D GAAA K K TTGA	T CCGG R CAA K TAC T TGTG V GGCTG L	H GAAA N GAT I CTC S GAT V CAAA K	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L	L AGA E TGT V AAAA N CCT L TTTT L CAA K	V GAA K GTG C TAA K GGT V ACC P AGA E	D GTA Y F F AAT I GGA E CCGG R AAT I	N TTAT I TTGC A TCC P CTAC T TCT L	G CTC S CCA Q C C GA E C C GA E C C GA E C C GA E C C GA E C C GA E L	CTG' 710 710 TGAG 770 AGGA 830 TGTG V 890 CGGA 0 010 ATGG C	H GCG R AGG G V TGC A CCG R TTC	G CAC T TGG G G G CCT L G G TCA H	TATT I AAAA K GGAA E GACA T GCCT P CCTA L
Y CCC P CAM Q GAC E GGC G TCC S GAC E TTM	I CACT T AGAT D SACT T CTCG S S GGAG E AACA	CCTGG L D 670 GTCG V E 730 TTCA S N 790 TTTGA L K 850 GGCCC G Q 910 CGCCG A V 970 GGAGA E T 1030	AAGC A ACTA Y AAGC A AGAT I ICAA K CTGA E	N AAAA K TGG G CAT I CGC A GGAA E GAG S	H GCT L TGGG G CAAA N TGAA D GAAA K W GGAAA	T CCGG R CAA K TAC T TGT V GCT L GAT AGA	H GAAA N GAT I CTC S GAT V CAAA K	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L 1050 IGGGGA	L AGA E TGT V AAAA N CCT L TTTT L CAA K	V GAA K GTG C TAA K V ACC P AGA E	D GTA Y TTTT F AAT I GGA E CCGG R AAT I	N TTAT  I TTGC A TTCC P CTAC T T TTCT L	G CTC S CCA Q CTTG C C GGA E GGT V 1 CCGA E 1	CTG' 710 710 TGAG 770 AGGA 830 TGTG V 890 CGAC C 010 ATGC C 176C	H GCCG R TGCCA R TCCGCR S TCCGCR	G CAC T TGG G G G CCT L G CT L TCA H CTC	TATT I AAAA K GGAA E GACA T GCCT P CCTA L
Y CCC P CAM Q GAC E GGC G TCC S GAC E TTM	I CACT T AGAT D SACT T CTCG S S GGAG E AACA	CCTGG L D 670 GTCG V E 730 TTCA S N 790 TTTGA L K 850 GGCCC G Q 910 CGCCG A V 970 GGAGA E T 1030	AAGC A ACTA Y AAGC A AGAT I ICAA K CTGA E	N AAAA K TGG G CAT I CGC A GGAA E GAG S	H GCT L TGGG G CAAA N TGAA D GAAA K W GGAAA	T CCGG R CAA K TAC T TGT V GCT L GAT AGA	H GAAA N GAT I CTC S GAT V CAAA K	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L	L AGA E TGT V AAAA N CCT L TTTT L CAA K	V GAA K GTG C TAA K V ACC P AGA E	D GTA Y TTTT F AAT I GGA E CCGG R AAT I	N TTAT  I TTGC A TTCC P CTAC T T TTCT L	G CTC S CCA Q CTTG C C GGA E I CGAA N	CTG' C 710 TGAC E 770 AGGA G 830 TGTC S 010 ATGC A TGC A	H GCCG R TGCCA R TCCGCR S TCCGCR	G CAC T TGG G G G CCT L G CT L TCA H CTC	TATT I AAAA K GGAA E GACA T GCCT P CCTA L
Y CCO P CAM Q GAO G G G G G T C T T T T T T	I CACT T AGAT D SACT CTCG S FTCT S FTCT T ACA T	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGCCG G Q 910 CGCCG'A V 970 GGAGA' E T 1030 AGTTA' V I 1090	AAGC AAGC AAGAT I ICAA K CTGA E ITAA K	N AAAA K TGG G CAT I CGCC A GGAA E GAAG S	H GCT L TGGG G CAAA N TGAA D GAAA K TTTGO W	T CCGG R CAA K TAC T TGT V GCT L I GAGAI E	H GAA N GAT I CTC S GAT V CAA K AGC A	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L 1050 IGGGGA' G D 1110	L AGA E TGT V AAAA N CCT L TTTT L CAA K	V GAA K GTG C TAA K V ACC P AGA E AAT	D GTA Y TTT F AAT I GGA E CCGG R AAT I V	N TTAT I TTGC A TTCC P CACC T T GAGG	G CTC S CCA C C C C C C C C C C C C C C C C	CTG' C 710 CTGAC E 770 AGGAC 830 CTGTC 890 CGTCC S 010 ATGC A 130	H GCCG R GCCG R CCCG R TTCC S	G CAC T TGG G GGT V CCT L GCT L TCA H CTC	H TATT I AAAA K GGAA E GACA T GCCT P CCTA L CTAC
Y CCO P CAM Q GAO G G G G G T C T T T T T T	I CACT T AGAT D SACT CTCG S FTCT S FTCT T ACA T	CCTGG L D 670 GTCG V E 730 TTCCA S N 790 TTTGA L K 850 GGCCG G Q 910 CGCCG'A V 970 GGAGA' E T 1030 AGTTA' V I 1090	AAGC AAGC AAGAT I ICAA K CTGA E ITAA K	N AAAA K TGG G CAT I CGCC A GGAA E GAAG S	H GCT L TGGG G CAAA N TGAA D GAAA K TTTGO W	T CCGG R CAA K TAC T TGT V GCT L I GAGAI E	H GAA N GAT I CTC S GAT V CAA K AGC A	TTTGCT L L 690 TCAGCT Q L 750 CCCCAT P I 810 CATCAA I K 870 CGCTAG A S 930 GCGCTT R F 990 ATGGCT W L 1050 IGGGGA G D	L AGA E TGT V AAAA N CCT L TTTT L CAA K	V GAA K GTG C TAA K V ACC P AGA E AAT	D GTA Y TTT F AAT I GGA E CCGG R AAT I V	N TTAT I TTGC A TTCC P CACC T T GAGG	G CTC S CCA C C C C C C C C C C C C C C C C	CTG' C 710 CTGAC E 770 AGGAC 830 CTGTC 890 CGTCC S 010 ATGC A 130	H GCCG R GCCG R CCCG R TTCC S	G CAC T TGG G GGT V CCT L GCT L TCA H CTC	H TATT I AAAA K GGAA E GACA T GCCT P CCTA L CTAC

Fig. 11 (Continuation)

		24	10						243	0					2	450			
AG.	AAA	CTT.	AGG	ACC	CAA	GAT	TAT	LAA	GCT	GCA	GAG	GAT	GCT	GAT	CGA'	rgt(	$\mathtt{GTT}$	CTT	CTTC
R		L		P					L							V		F	F
		24	70						249	0					2	510			
CT	GTT	CCT	CTT'	TGC	GGT	GTG	GAT	GGI	GGC	CTT	TGG	CGT	GGC	CAG	GCA	AGG	GAT	CCT	TAGG
L	F	L	F	A	v	W	M	v	Α	F	G	V	Α	R	Q	G	I	L	R
		25							255	_					_	570			
CA	GAA	TGA	GCA	GCG	CTG	GAG	GTG	GAI	TTA	CCG	TTC	GGT	CAT	CTA	CGA	GCC	CTA	CCT	GGCC
Q	N	E	Q	R	W	R	W	I	F	R	S	V	I	Y	E	P	Y	L	A
		25							261	-					_	630			
ΑT	GTT	CGG	CCA	GGI	GCC	CAG	TGA	CGT	GGA	TGG	TAC	CAC	GTA	TGA	CTT	TGC	CCA	CTG	CACC
M	F	G	Q	V	P	s	D	V	D	G	T	T	Y	D	F	A	H	C	T
		26							267	-					_	690			
TT	CAC	TGG	GAA	TGA	GTC	CAA	GCC	ACI	GTG	TGT	GGA	GCT	GGA	TGA	GCA	CAA	CCT		CCGG
$\mathbf{F}$	T	G	N	E	s	K	P	L	C	V	E	L	D	E	H		L	P	R
		27							273	-					_	750			
$\mathbf{T}\mathbf{T}$	CCC	CGA	GTG	GAI	CAC	CAT	CCC	CCI	GGT	GTG	CAT	CTA	CAT	GTT					CCTG
F	P	E	W	I	$\mathbf{T}$	I	P	L	V	C	I	Y	M	· L	_	${f T}$	N	Ι	L
		27							279						_	810			
CT	GGT	CAA	CCT	GCI	GGT	CGC	CAT												CAAT
L	V	N	L	L	V	A	M	F	G	_	T	V	G	${f T}$	V	-	E	N	N
		28							285	-					_	870			
GΑ	.CCA																		CAAT
D	Q	V		K	F	Q	R	_	F		V	Q	$\mathbf{E}$	Y	_	s	R	L	N
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																			CAAG
Ι	P	F	-	F	I	V	F	A	Y		Y	M	V	V		K	C	F	K
		29				· <b>_</b>			297	_			~~~		_	990	ma x	7 (7)	(1) N (1)
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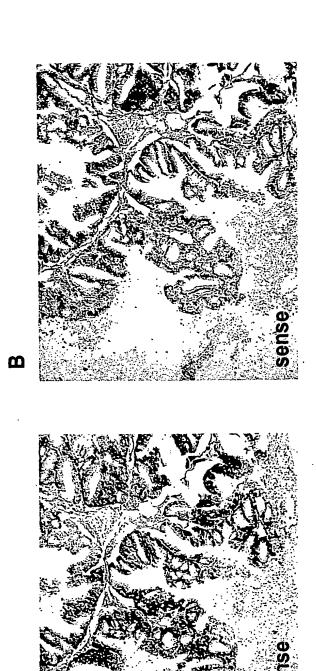
## b.) Trp10 protein:

MKSFLPVHTIVLIRENVCKCGYAQSQHMEGTQINQSEKWNYKKHTKEFPTDAFGDIQFETLGKKGKYIRLSCDTDAEILY ELLTQHWHLKTPNLVISVTGGAKNFALKPRMRKIFSRLIYIAQSKGAWILTGGTHYGLMKYIGEVVRDNTISRSSEENIV AIGIAAWGMVSNRDTLIRNCDAEGYFLAQYLMDDFTRDPLYILDNNHTHLLLVDNGCHGHPTVEAKLRNQLEKYISERTI QDSNYGGKIPIVCFAQGGGKETLKAINTSIKNKIPCVVVEGSGQIADVIASLVEVEDALTSSAVKEKLVRFLPRTVSRLP EEETESWIKWLKEILECSHLLTVIKMEEAGDEIVSNAISYALYKAFSTSEQDKDNWNGQLKLLLEWNQLDLANDEIFTND RRWESADLQEVMFTALIKDRPKFVRLFLENGLNLRKFLTHDVLTELFSNHFSTLVYRNLQIAKNSYNDALLTFVWKLVAN FRRGFRKEDRNGRDEMDIELHDVSPITRHPLQALFIWAILQNKKELSKVIWEQTRGCTLAALGASKLLKTLAKVKNDINA AGESEELANEYETRAVELFTECYSSDEDLAEQLLVYSCEAWGGSNCLELAVEATDQHFIAQPGVQNFLSKQWYGEISRDT KNWKIILCLFIIPLVGCGFVSFRKKPVDKHKKLLWYYVAFFTSPFVVFSWNVVFYIAFLLLFAYVLLMDFHSVPHPPELV LYSLVFVLFCDEVRQWYVNGVNYFTDLWNVMDTLGLFYFIAGIVFRLHSSNKSSLYSGRVIFCLDYIIFTLRLIHIFTVS RNLGPKIIMLQRMLIDVFFFLFLFAVWMVAFGVARQGILRQNEQRWRWIFRSVIYEPYLAMFGQVPSDVDGTTYDFAHCT FTGNESKPLCVELDEHNLPRFPEWITIPLVCIYMLSTNILLVNLLVAMFGYTVGTVQENNDQVWKFQRYFLVQEYCSRLN IPFPFIVFAYFYMVVKKCFKCCCKEKNMESSVCCFKNEDNETLAWEGVMKENYLVKINTKANDTSEEMRHRFRQLDTKLN DLKGLLKEIANKIK

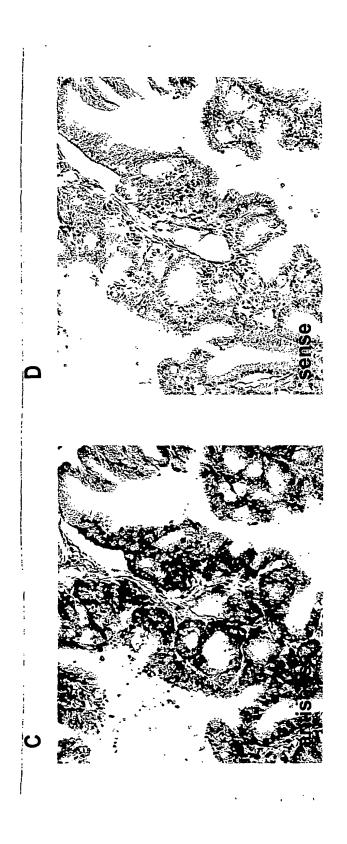
Figs. 12A and 12B

## The Trp8 gene is expressed in endometrial or uterine cancer, but not in normal endometrium

Endometrial cancer:



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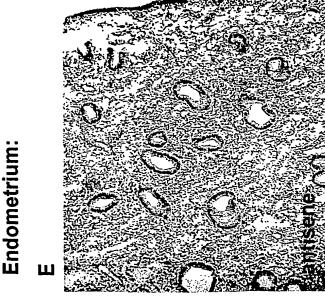


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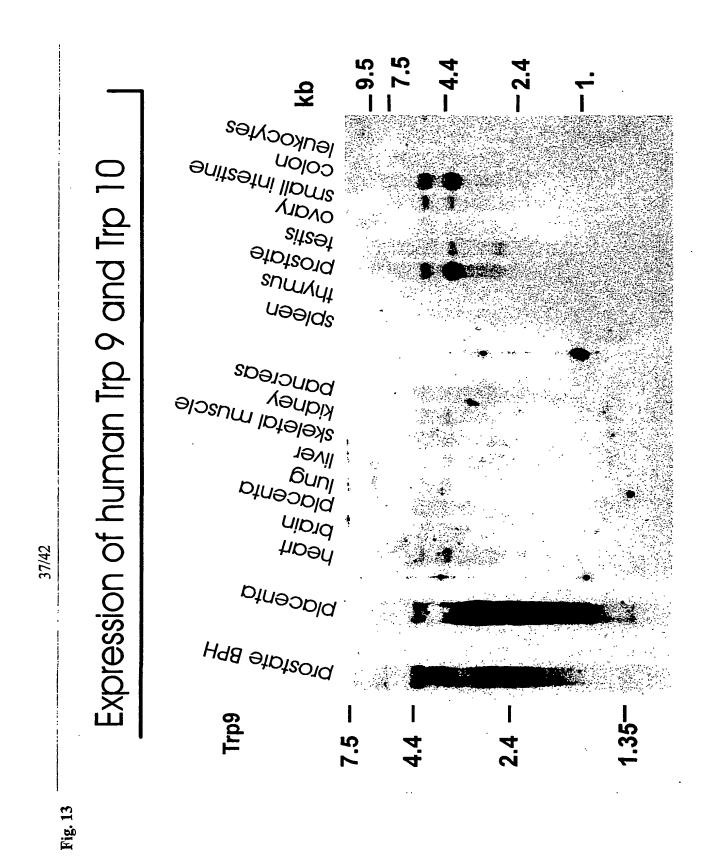
Figs. 12C and 12D

Endometrium:

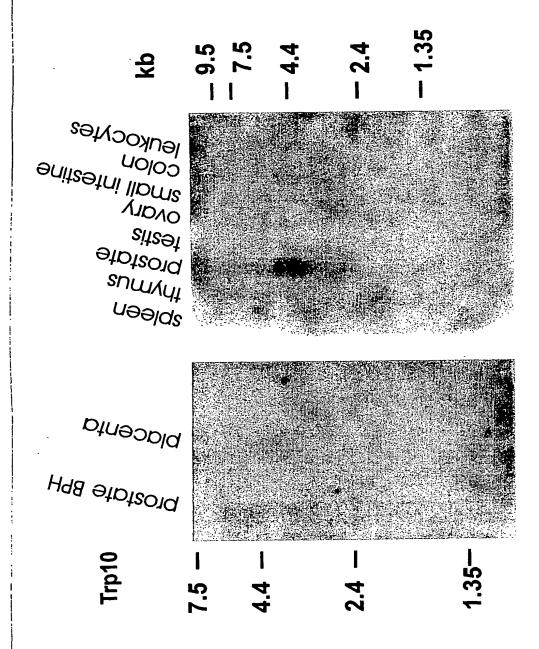
Figs. 12E and 12F



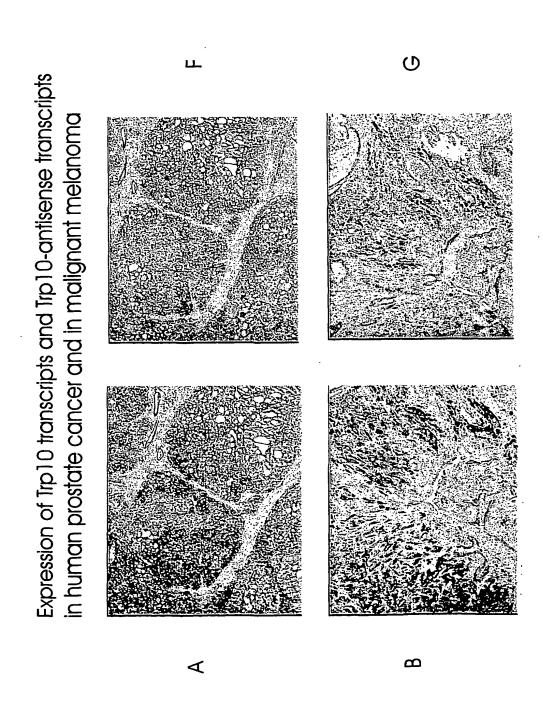
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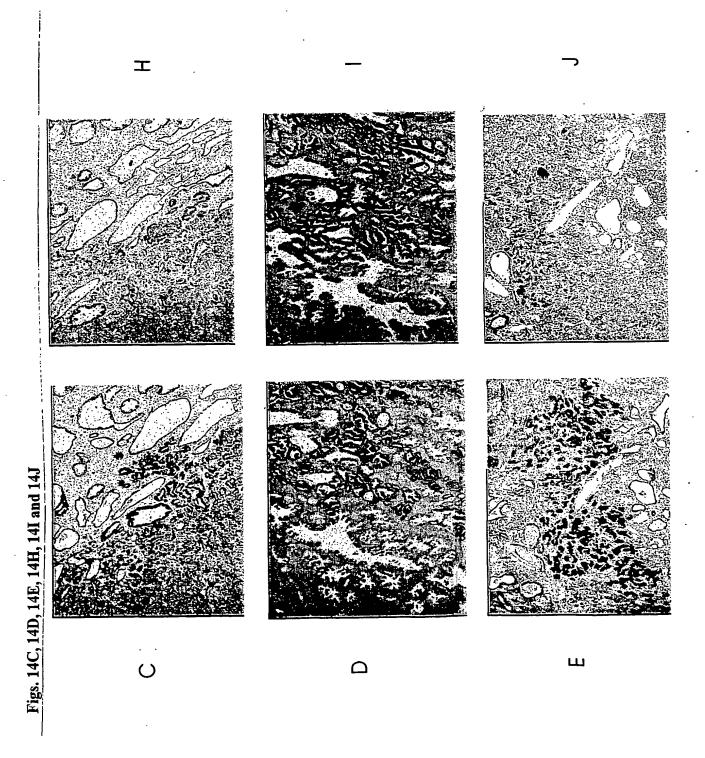


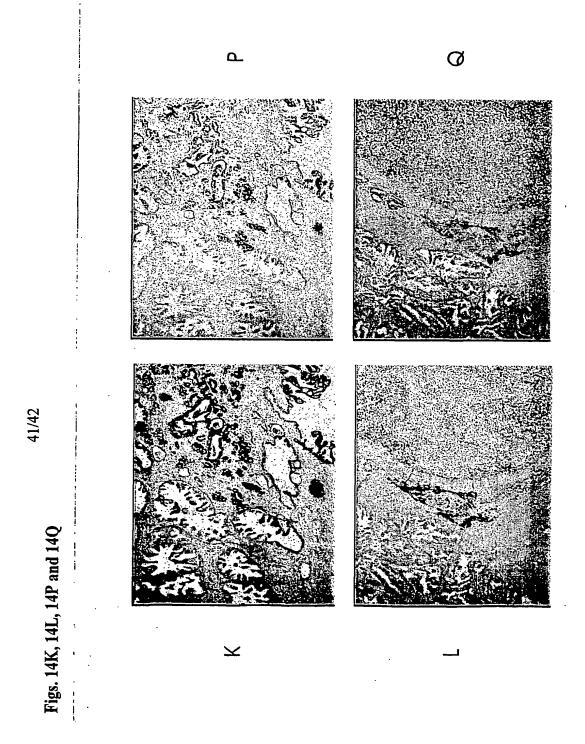




Figs. 14A, 14B, 14F and 14G







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- (74) Agent: HUBER, Bernard; Huber & Schüssler, Truderinger Str. 246, 81825 München (DE).

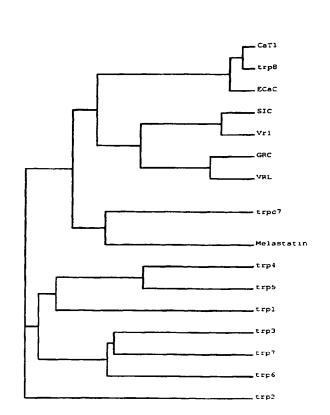
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[Continued on next page]

#### (54) Title: TRP8, TRP9 AND TRP10, MARKERS FOR CANCER



(57) Abstract: The present invention relates to gene expression in normal cells and cells of malignant tumors and particularly to novel markers associated with cancer, Trp8, Trp9 and Trp10, and the genes encoding Trp8, Trp9 and Trp10. Also provided are vectors, host cells, antibodies, and recombinant methods for producing these human proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating a tumor.

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C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  $IPC\ 7\ C07\,K$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, SEQUENCE SEARCH, WPI Data, PAJ

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х	WO 99 09166 A (SHAPERO MICHAEL H ;DENDREON CORP (US); LAUS REINER (US); TSAVALER) 25 February 1999 (1999-02-25) see SEQID14 + 15, pages 2,3, 28,29, Example 4 table 3		1-10, 12-17, 23,29-31
х	WO 00 40614 A (BETH ISRAEL HO; SCHARENBERG ANDREW M (US)) 13 July 2000 (2000-07-13) see seqid31 + 32, page 11, fi paragraph, page 44, lines 13-	rst	1-10,12, 31
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<u> </u>	her documents are listed in the continuation of box C. ttegories of cited documents:	*** tates document published after the inte	ernational filing date
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rational Application No
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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Internal Control
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MULLER D ET AL: "Molecular cloning, tissue distribution, and chromosomal mapping of the human epithelial Ca2+ channel (ECAC1)." GENOMICS, vol. 67, no. 1, 1 July 2000 (2000-07-01), pages 48-53, XP002222953 ISSN: 0888-7543 the whole document	1
X	WO 98 15657 A (ABBOTT LAB) 16 April 1998 (1998-04-16) the whole document	1-12, 29-31
Х	WO 98 37093 A (CORIXA CORP) 27 August 1998 (1998-08-27) the whole document	1-12, 29-31
A	TSAVALER LARISA ET AL: "TRP-P8, a novel prostate-specific gene, is upregulated in prostate cancer and other malignancies and shares high homology with TRP calcium channel proteins."  PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 694 XP008011242  91st Annual Meeting of the American Association for Cancer Research.;San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X the whole document	
A	HARTENECK C ET AL: "FROM WORM TO MAN: THREE SUBFAMILIES OF TRP CHANNELS" TRENDS IN NEUROSCIENCE, ELSEVIER, AMSTERDAM, NL, vol. 23, no. 4, April 2000 (2000-04), pages 159-166, XP001012870 ISSN: 0166-2236	
P,X	WO 01 14423 A (SMITHKLINE BEECHAM PLC)  1 March 2001 (2001-03-01)  see SEQid1 + 2; see example 1  -/	1-9,31

Form PCT/ISA/210 (continuation of second sheet) (July 1952)

national Application No
PCT/EP 01/08309

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Retainent to claim No.
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
P,X	WISSENBACH ULRICH ET AL: "Expression of CaT-like, a novel calcium-selective channel, correlates with the malignancy of prostate cancer." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 22, 1 June 2001 (2001-06-01), pages 19461-19468, XP002222954 ISSN: 0021-9258 the whole document	1-9,13, 14, 16-19, 21-23,29
P,X	WO 01 04303 A (HEDIGER MATTHIAS A) 18 January 2001 (2001-01-18) see SEQID1 + 2 the whole document	1-5
P,X	WO 01 42467 A (MILLENNIUM PREDICTIVE MEDICINE) 14 June 2001 (2001-06-14) see SEQID 4615	1
E	WO 01 51633 A (FANGER GARY RICHARD; HARLOCKER SUSAN L (US); MEAGHER MADELEINE JOY) 19 July 2001 (2001-07-19) see SEQID764, example 3, claims	1
E	WO 02 14361 A (AGENSYS INC) 21 February 2002 (2002-02-21) see SEQID1479, examples 1-4 the whole document	1-10, 13-23
E	WO 02 00722 A (SILOS SANTIAGO INMACULADA; CURTIS RORY A J (US); MILLENNIUM PHARM) 3 January 2002 (2002-01-03) see SEQID4	1-5
Ε	WO 01 68857 A (CURTIS RORY A J ;COOK WILLIAM JAMES (US); MILLENNIUM PHARM INC (US) 20 September 2001 (2001-09-20) see SEQID1, examples	1-5
	WO 01 53348 A (SQUIBB BRISTOL MYERS CO; GAUGHAN GLEN T (US); RAMANATHAN CHANDRAS) 26 July 2001 (2001-07-26) see SEQID5 the whole document	1
	WO 01 62794 A (LORA JOSE M ; CURTIS RORY A J (US); GLUCKSMANN MARIA ALEXANDRA (US)) 30 August 2001 (2001-08-30) the whole document	1-9
	WO 02 30268 A (EOS BIOTECHNOLOGY INC) 18 April 2002 (2002-04-18) see SEQID53	1,6
	-/	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

national Application No PCT/EP 01/08309

		PC1/EP 01/08303	
C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
T	BOEDDING MATTHIAS ET AL: "The recombinant human TRPV6 channel functions as Ca2+ sensor in human embryonic kidney and rat basophilic leukemia cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 39, 27 September 2002 (2002-09-27), pages 36656-36664, XP002222955 September 27, 2002 ISSN: 0021-9258 the whole document		
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nternational application No. PCT/EP 01/08309

#### INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  Although claims 24-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X Claims Nos.: 12 partially because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
1. X As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

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#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12, 29-31 partially, 13-28 completely

Isolated nucleic acid molecules encoding human prostate carcinom associated proteins as characterized by SEQIDS5,45,11,3 and SEQIDs 6,46,12,4, respectively; the recombinant expression of the same in host cells; the isolated proteins as characterized by SEQIDs 6,46,12,4; antisense RNA sequence and ribozyme complementary to said nucleic acid molecules; inhibitor that can suppress the activity of said prostate carcinom associated proteins; method for diagnosing a prostate carcinoma by contacting a sample with a nucleic acid, an antibody or other reagent that reacts with the mRNA of SEQIDs5,45,11,3; method for diagnosing endomertial cancer by contacting a target sample with a nucleic acid, an antibody or other reagent that reacts with the mRNA of SEQIDs5,45,11,3; method for diagnosing a melanoma, chorion carcinoma, cancer of the lung and ot the prostate comprising contacting a target sample with a reagent which detects antisense RNA of SEQIDs 11 and 3; method for preventing prostate tumour, endometrial cancer, choroin carcinoma or cancer of the lung comprising administering an inhibiting reagent of human prostate carcinom associated proteins; diagnostic kit containing an antibody; method for identifyng an agonist or an antagonist of human prostate carcinom associated proteins.

2. Claims: 1-12, 29-31 partially

Isolated nucleic acid molecule encoding human prostate carcinom associated protein as characterized by SEQIDs 7 and SEQIDs 8, respectively; the recombinant expression of the same in host cells; the isolated protein as characterized by SEQIDs 8; antisense RNA sequence and ribozyme complementary to said nucleic acid molecule; inhibitor that can suppress the activity of said prostate carcinom associated protein; diagnostic kit containing an antibody; method for identifyng an agonist or an antagonist of human prostate carcinom associated proteins.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12 partially

Present claim 12 relates to an inhibitor wich is defined by reference to a desirable characteristic or property, namely suppressing the activity of the protein of claim 6.

The claims cover all inhibitors having this characteristic or property, whereas the application provides only support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for a limited number of such inhibitors.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the inhibitors by reference to a result to be achieved.

Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claim 12 which appear to be clear, supported and disclosed, namely those parts relating to the Trp8/10 corresponding antibody, Trp8/10 corresponding antisense construct, a Trp8/10 corresponding ribozyme.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Information on patent family members

rnational Application No PCT/EP 01/08309

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9909166 A	25-02-1999	US AU CA EP JP NZ WO	6194152 B1 744875 B2 9021898 A 2300364 A1 1005549 A2 2001514889 T 503404 A 9909166 A2	27-02-2001 07-03-2002 08-03-1999 25-02-1999 07-06-2000 18-09-2001 01-03-2002 25-02-1999
WO 0040614 A	13-07-2000	AU CA EP JP WO	2055600 A 2360396 A1 1141017 A2 2002536966 T 0040614 A2	24-07-2000 13-07-2000 10-10-2001 05-11-2002 13-07-2000
WO 9815657 A	16-04-1998	US EP JP WO US	5919638 A 0954599 A1 2001523948 T 9815657 A1 6110675 A	06-07-1999 10-11-1999 27-11-2001 16-04-1998 29-08-2000
WO 9837093 A	27-08-1998	US AU BR CN CZ EP HO NZ PL VS US US US US US US US	6261562 B1 731840 B2 6181898 A 9808881 A 1252837 T 9903016 A3 1005546 A2 0002095 A2 994069 A 337446 A 335348 A1 9902053 T2 6262245 B1 9837093 A2 2002090372 A1 6465611 B1 6395278 B1 6329505 B1 2002022248 A1 2002051977 A1 2002193296 A1 9801585 A	17-07-2001 05-04-2001 09-09-1998 11-09-2001 10-05-2000 13-03-2002 07-06-2000 28-10-2000 22-10-1999 23-02-2001 25-04-2000 21-04-2000 17-07-2001 27-08-1998 11-07-2002 15-10-2002 28-05-2002 11-12-2001 21-02-2002 02-05-2002 04-09-1998
WO 0114423 A	01-03-2001	WO	0114423 A1	01-03-2001
WO 0104303 A	18-01-2001	AU EP WO	5778600 A 1194546 A1 0104303 A1	30-01-2001 10-04-2002 18-01-2001
WO 0142467 A	14-06-2001	AU WO	2074201 A 0142467 A2	18-06-2001 14-06-2001
WO 0151633 A	19-07-2001	AU AU WO EP EP	3447401 A 6158700 A 0104143 A2 1194571 A1 1261708 A2	24-07-2001 30-01-2001 18-01-2001 10-04-2002 04-12-2002

Form PCT/ISA/210 (patent family annex) (July 1992)

Information on patent family members

mational Application No
PCT/EP 01/08309

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0151633 A		NO WO US US	20023402 A 0151633 A2 2002022248 A1 2002051977 A1 2002193296 A1	29-08-2002 19-07-2001 21-02-2002 02-05-2002 19-12-2002
WO 0214361 A	21-02-2002	AU WO	8501801 A 0214361 A2	25-02-2002 21-02-2002
WO 0200722 A	03-01-2002	AU WO US	7024001 A 0200722 A2 2002156253 A1	08-01-2002 03-01-2002 24-10-2002
WO 0168857 A	20-09-2001	AU WO	4746001 A 0168857 A2	24-09-2001 20-09-2001
WO 0153348 A	26-07-2001	AU EP WO US	3648201 A 1252189 A2 0153348 A2 2002072101 A1	31-07-2001 30-10-2002 26-07-2001 13-06-2002
WO 0162794 A	30-08-2001	AU WO US	3859601 A 0162794 A2 2002142377 A1	03-09-2001 30-08-2001 03-10-2002
WO 0230268 A	18-04-2002	US AU WO	2002068036 A1 1534502 A 0230268 A2	06-06-2002 22-04-2002 18-04-2002

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